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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.

Topics to be covered in our next issue:

- Hemispherectomy and radio-frequency thalamotomy in treatment of epilepsy
- Identification of cranial nerves in endonasal surgery
- Neurosurgical interventions in patients receiving dual antiplatelet therapy
The Use of Intraoperative Neuroimaging Tools and a Navigation System in Surgical Treatment of Primary and Metastatic Spinal Tumors


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Introduction. Surgical treatment of spinal tumors is associated with a high risk of intraoperative complications, including injury to the spinal cord, its roots, and large vessels both during tumor resection and at the stabilization stage during implantation of pedicle or corporal screws. The use of intraoperative neuroimaging tools and a navigation system in surgical treatment of spinal tumors enables identifying the location and extension of a tumor lesion directly in the operating room, thus ensuring control over the resection area and the possibility of stabilizing the spine under disturbed anatomy conditions when bone density is altered by the osteolytic process or systemic changes. The risk of injury to the major blood vessels is also reduced.

Material and methods. Surgical treatment of 156 patients with primary and metastatic spinal tumors was performed at the Burdenko Neurosurgical Institute over the period between 2002 and December 2014. Twelve patients underwent diagnostic intervention (transcutaneous biopsy): 35 patients underwent surgery using intraoperative CT with the navigation system. The indication for performing a biopsy using both CT and the navigation system was the presence of a spinal tumor not verified by pathomorphological examination. An O-arm intraoperative computed tomography scanner and a Medtronic’s StealthStation S7 Navigation System were used in all cases.

Conclusions. The use of both CT and the navigation system provides high-quality treatment and significantly reduces radiation exposure to the medical personnel and patients. The possibility of intraoperative identification of tumor location and extension in the bone tissue facilitates adequate tumor resection within the intact surgical margin, with the surrounding vessels and neurological structures being under real-time control.

Keywords: intraoperative computed tomography scanner, navigation system, safety, surgical treatment quality, primary and metastatic spinal tumors.

Surgical treatment of spinal tumors is associated with a high risk of intraoperative complications, including injury to the spinal cord, its roots, and large vessels both during tumor resection and at the stabilization stage when implanting pedicle or corporal screws [1—4]. In the literature devoted to spinal surgery, the altered topographic anatomy and the disturbed "standard" landmarks resulting from the osteolytic process and tumor growth are considered to be the reasons for these complications. Under these conditions, it is not always possible to perform surgical intervention without using intraoperative imaging; sometimes it can even be dangerous [5, 6]. X-ray filming using the mobile C-arm X-ray machine (also known as an electron optical image converter) is the most common method for intraoperative imaging. The electron optical image converter produces 2D images; it has started to be routinely used over the past decade. The main problems that can be solved by C-arm include preoperative mapping (identifying the zones of interest), positioning tools during puncture procedures, and ensuring the adequate positioning of the inserted implants. The drawbacks of the electron optical image converter include the fact that horizontal plane images cannot be recorded; furthermore, it is a source of radiation exposure for the patient and medical personnel [6].

Current advances in imaging techniques allow one to perform intraoperative computed tomography. An intraoperative CT (iCT) scanner that can be integrated into navigation systems has been designed for this purpose. This technology is most widely used during implantation of transpedicular screws [8—10].

There have been few reports about using robot-assisted technologies that allow one to pass a surgical instrument via a complex trajectory without additional radiographic monitoring in literature. These technologies allow one to increase the effectiveness of biopsy in vertebral tumors and placement of screws for various types of fixing functional spinal units. The Spine Assist Mazor robotic assistance system is one of the tools used in Russia; it enables intraoperative monitoring of the trajectory of delivering instruments and implants into the vertebral bodies [11—14]. A drawback of this method is that preoperative planning using MSCT is needed, while the spinal region accessible for this technology is limited (from the thoracic vertebra T3 to the sacrum) [15]. Furthermore, the functional significance of iCT in combination with the navigation system is not limited only to screw placement.

Unlike the passive robot-assistance systems for monitoring instrument positioning in the wound, the use of intraoperative neuroimaging tools and the navigation system during surgical treatment of spinal tumors makes it possible to identify localization and extention of tumor lesions directly during the surgery. This allows one to control the resection area and makes it possible to stabilize the spine in patients with disturbed anatomy when density of bone tissue is altered by the osteolytic process.

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process or systemic changes. The risk of damaging large vessels also decreases [2, 3, 6].

Introduction of high-tech intraoperative instruments into modern surgical practice, accumulation of the vast surgical experience in treating primary and metastatic spinal tumors, and development of new surgical approaches minimize the risk of complications and improve treatment quality.

This study was aimed at evaluating the use of the intraoperative CT scanner and the navigation system in diagnosing and treating primary and metastatic spinal tumors.

Materials and Methods

Surgical treatment of 156 patients with primary and metastatic spinal tumors was performed at the Burdenko Neurosurgical Institute over the period between 2002 and 2014. iCT and the modern navigation system have been used at the Department of Spinal Neurosurgery since August 2013. During this period, 12 patients underwent diagnostic intervention (transcutaneous biopsy); 35 patients underwent surgery using intraoperative CT and the navigation system. The study group included 45 patients (18 males and 27 females); mean age was 49.6 years (range: 15 to 80 years). Table shows the distribution of patients with respect to the type of surgical intervention performed.

The indication for performing a diagnostic procedure using iCT and the navigation system was the presence of a spinal tumor without history of cancer and the presence of a known primary metastatic focus. MRI and SCT signs of compression of the neural structures and the disturbed static balance of the spine were indications for decompression and stabilization surgeries.

An O-arm intraoperative computed tomography scanner and a Medtronic’s StealthStation S7 Navigation System were used in all cases (Fig. 1). This neuroimaging and navigation system consists of five components: a workstation with a display, a platform for intraoperative imaging with a mobile scanning unit (gantry), a navigation station equipped with a camera, and a display showing the navigation. In technical terms, no matter what the manufacturer is, the neuronavigation system is a computer-controlled two-sided antenna with a system of marker devices.

Intraoperative 2D and/or 3D CT scanning is carried out during the surgery, immediately prior to skin incision, to accurately identify the surgical site. Next, the reference frame is tightly secured in the patient’s body (to a spinous process or to the iliac crest) next to the surgical site and 3D CT scanning is performed. The CT data are then transmitted to the navigation station and tools are registered with light emitting diodes or reflective spheres and the accuracy of the resulting images is verified using a probe. The navigation probe is placed onto a skeletonized vertebral portion that can be clearly visualized. If the data about probe position shown on the navigation display mismatch what an eye sees in the surgical wound, registration needs to be carried out once again. Next, the main stage of navigation starts. A surgeon uses special tools to obtain information about tumor location and extension, as well as positioning of tools and implants in real time. If needed, the surgeon can use any pre-calibrated instrument in addition to the conventional set of tools.

Let us discuss the case of using O-arm iCT with navigation system to resect a spinal tumor.

A 40-year-old female patient K. was diagnosed with myelomatosium presenting as: multiple spinal lesions, pathological fractures of the T2, T6 vertebral bodies, spinal cord compression at the T6 level, myelopathy, spastic paraparesis of the lower extremities, and pelvic floor dysfunction (Fig. 2). The neurological status upon admission included paraplegia of the lower extremities, bilateral conductive-type sensitive disorder starting from the T6 level, and pelvic floor dysfunction (urinary retention).

Surgical intervention involved decompression at the T5—T7 level, resection of the tumor in the T6 vertebral body, and transpedicular stabilization at the level of the T4—T5—T7—T8 vertebrae using iCT with the navigation system (Figs. 3, 4, 5).

Positioning of the vertebral screws in the vertebral body was controlled in real time, thus making it possible to avoid implant malpositioning.

After the surgery, patient’s leg muscle strength increased to score 3 for proximal muscles and to score 4, for distal muscles; the function of the pelvic floor was recovered.

Histological examination showed plasmocytoma. The patient postoperatively underwent six courses of chemotherapy. Follow-up MRI and SCT scanning of the thoracic spine showed no signs of spinal cord compression and satisfactory positioning of the stabilization system (Fig. 6).

Surgical management of primary bone tumors is often associated with the risk of tumor recurrence because there are no visible landmarks and it is difficult to interpret tumor remnants intraoperatively.

Let us discuss a clinical case of using intraoperative CT with the navigation system in a 39-year-old male patient O. diagnosed with osteoid ostema of the L5 vertebral body. Severe local pain in the lumbar spine was the indication for surgery. The neurological status included local pain in the absence of any motor or sensory problems. SCT scanning of the lumboSacral spine showed an osteoid ostema of the L5 vertebral body (Fig. 7).

Microsurgical resection of the osteoid ostema of the L5 vertebral body was performed on the left side through the intralaminar approach under control of iCT with the navigation system (Fig. 8).

The postoperative period was not accompanied by any complications; no worsening of the neurological
symptoms was observed. Intraoperative CT scanning of the lumbosacral spine showed no signs of tumor remnants.

**Results**

We analyzed the use of iCT with the navigation system in diagnosis and treatment of primary and metastatic spinal tumors.

When performing transcutaneous interventions (biopsy and vertebroplasty), iCT with the navigation system was used to determine tumor localization and its spread into the bone tissue and to perform intraoperative control over accuracy of instrument positioning. It has been demonstrated that this procedure reduces the risk that there will be no tumor cells in the biopsy. A significant advantage of using this method in vertebroplasty is that filling a vertebra with bone cement is monitored not only using the conventional 2D images but also based on the 3D CT data.

Intraoperative computer-assisted navigation used during resection of spinal tumors enables real-time control over the completeness of tumor resection and ensures safety of tumor resection due to high-quality imaging of its margin, the adjacent blood vessels, and vital organs, especially when performing en bloc resection.

iCT with the navigation system was used during the stabilization stage of the surgery that required implant placement in order to intraoperatively control the accuracy of implant insertion and the decompression zone. 3D scanning and 3D reconstruction were carried out after the surgery had been finished.

We find using iCT with the navigation system especially useful when surgical management is carried out in patients with disturbed anatomy when density of the bone tissue is altered by either the oncological process or systemic changes and 2D imaging fails to visualize the resection area. In order to assess the accuracy of implanting pedicular screws using iCT with the navigation system, we developed an original scale, where 3 groups have been differentiated based on the presence of perforation of the cortical layer of the vertebral arch root: group 1 (the optimal screw position) — no perforation made at all; group 2 (a satisfactory screw position) — the screw is positioned outside the vertebral arch root by less than 2 mm; and group 3 (an unsatisfactory screw position) — the screw is placed outside the cortical layer of the vertebral arch root by more than 2 mm.

Within this study, we have placed 80 transpedicular screws; 78 (97.5%) of them were characterized by the optimal placement (group 1) and 2 (2.5%), by satisfactory positioning (group 2). No unsatisfactory positioning of screws has been detected, since control CT study was performed in the operating room immediately after the implants had been placed.

We assessed the accuracy of placement of prosthetic vertebral bodies for interbody stabilization using iCT.

### Distribution of patients with respect to the type of diagnostic and surgical procedures

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Number of surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcutaneous biopsy of spinal tumors</td>
<td>12</td>
</tr>
<tr>
<td>Vertebroplasty/biopsy+vertebroplasty</td>
<td>14</td>
</tr>
<tr>
<td>Resection of spinal tumors with intraoperative monitoring over the resection area</td>
<td>8</td>
</tr>
<tr>
<td>Resection of spinal tumors and spine stabilization</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
</tr>
</tbody>
</table>
Fig. 2. Preoperative sagittal and axial T2WI scans of the cervical, thoracic, and lumbosacral spine.

a, b — signs of multiple spinal lesions: pathologic fracture of the T2 vertebral body without signs of spinal cord compression; c, d — tumor of the T6 vertebral body with signs of pathologic fracture and severe spinal cord compression at this level; e, f — tumor of the lateral sacral mass.

Fig. 3. Intraoperative stagewise control over the trajectory of instrument positioning (a) and placement of transpedicular screws (b) at the level of T4–T5–T7–T8 vertebrae using the navigation system.
Fig. 4. Intraoperative CT examination in the 3D scanning mode. 

a — control over the decompression zone and volume of the tumor being resected; b — control over positioning of transpedicular screws.

Fig. 5. Postoperative spondylograms of the thoracic spine: the lateral (a) and anteroposterior (b) view.

with the navigation system based on their position with respect to the adjacent vertebral bodies and presence of the physiologic spinal curve. Five prosthetic vertebral bodies were inserted. Neither improper position of the implants nor instability during the postoperative period has been detected.

We analyzed the surgery durations. Within the first months, surgical interventions lasted a rather significant time, since we only started to master the iCT method. The surgery duration tended to decrease as new skills were acquired.

Discussion

In modern spinal surgery, navigation holds a prominent place among the methods for treating degenerative spine disorders. First of all, this method is used during implantation of stabilization constructs. iCT allows one to reduce radiation exposure both to patient and the surgical team compared to using the C-arm; it also has a number of advantages that make placement of transpedicular screws and cages simpler [1].

The use of neuroimaging and the navigation system in treatment of cancer patients is relatively new, since we
have found only few publications of foreign researchers devoted to this topic.

Van Royen et al. [16] reported a case of treating a 17-year-old girl with severe scoliosis and pain syndrome who had been diagnosed with osteoid osteoma at the T9 level. The problem of tumor excision was associated with the need to retain the supporting function of the spine after total resection of the tumor. Curettage is the method of choice for resecting this type of tumors. High-speed bur with a reference frame was used to perform this task. This procedure made it possible to monitor the depth of bur immersion in real time and to control the adjacent structures. R. Moore [6] used the navigation system to control the completeness of resection of the osteoid osteoma at the C7 level using hemilaminectomy for approaching the resection area. M. Sheila, Smitherman, et al. [17] reported a case of excision of a giant cell tumor involving the ribs at the T4—T7 level via en bloc resection. The tumor was resected radically; navigation was used to monitor and place the transpedicular system.

The main task of surgical treatment of spine tumors is to either improve or maintain patient’s quality of life. The navigation-assisted intraoperative neuroimaging system makes it possible to improve the quality of treatment by minimizing the risk of intraoperative complications and to increase safety of surgical interventions.

Quality and accuracy of iCT images that allow one to correct screw positioning during stabilization surgeries in real time eventually minimize the possible intraoperative complications and reduce radiation exposure to medical personnel and patients.
Conclusions

The simultaneous use of iCT and the navigation system ensures high-quality treatment and significantly reduces radiation exposure to medical personnel and patients. The possibility to intraoperatively identify the position and extension of the tumor in the bone tissue allows one to perform adequate resection by real-time monitoring of the position of tools with respect to the surrounding vessels and neural structures.

This method is very important when radical resection of vertebral tumor is needed, as well as in all the cases of surgical stabilization of the spine in patients with altered anatomy and density of bone tissue.

CT-based navigation technologies expand surgical capacity by improving quality and safety of surgical treatment of cancer patients.

Authors declare no conflict of interest.
There has already been a rather long history of using intraoperative navigation tools for implantation of pedicular screws in oncovebrological practice. However, no data on the effectiveness of stabilizing surgeries using the navigation system enabling intraoperative monitoring of screw position have been reported thus far. The use of iCT scanning and the navigation system during identification and resection of bone tumors is a modern and relevant method that would improve the effectiveness of surgery, while simultaneously reducing the injury rate among patients and probably increasing the relapse-free period in patients with conventionally malignant and locally aggressive tumors.

Patients with disseminated lesions receive surgical treatment in oncological practice rather rarely. The conventional strategies for managing patients with this pathology include drug therapy and/or radiation therapy, which affect quality of life to the largest extent.

Surgical aggression in treatment of patients with multiple spinal lesions needs to be reduced because this type of management is associated with a high injury rate, while showing a relatively low effect on neurological deficit and having no effect on the overall survival rate. Meanwhile, the timely performed surgical aid to the patients whose favorable outcome is caused by the positive response to chemotherapy has a significant effect on quality of life and often, on patients’ survival.

Although being mentioned in publications relatively rarely, the malposition of pedicle screws is a rather common problem in vertebrological practice. It usually results in neuropathy caused by compression of spinal cord or its roots, thus aggravating patient’s condition that is already rather bad.

Today, resection of bone tumors using iCT navigation is the method of choice as it allows real-time monitoring of tumor edges and adequate resection of the tumor without the risk of damaging the tumor capsule. This publication unquestionably is topical, since it demonstrates the possibility of reducing the injury rate of the surgery and avoiding a number of complications associated with placement of pedicle screws in patients with altered anatomy.
Commentary

The technologies for navigation-controlled placement of spine stabilization systems are currently widely used by neurosurgeons, orthopedists, and onco-vertebrologists all over the world. However, this method is new for Russian surgeons. Implantation of pedicle screws is used to recover the supporting function of the spine in patients with injuries, degenerative spine disorders, or spinal tumors. Studies focused on using iCT and the navigation system in surgery of spinal tumors is new for Russian publications. Until recently, no studies that would demonstrate the effectiveness of performing stabilization surgeries using the navigation system enabling intraoperative monitoring of screw position have been published. The use of iCT and the navigation system during identification and resection of bone tumors is a modern and relevant technique that would unquestionably increase the effectiveness of surgeries and reduce the risk of surgical injury.

The problem of malposition of pedicle screws is also discussed in this study. It is rather common in vertebrology, although little attention has been paid to this problem in publications. This complication results in chronic pain, paresis of extremities, and pelvic floor dysfunction. Unfortunately, the authors did not provide any information about the control group of patients with screw malposition and did not mention the main reasons for the failure, although they demonstrated the effectiveness of using iCT with the navigation system.

Today, resection of bone tumors using iCT navigation is the method of choice, since it allows one to adequately remove tumor without the risk of damaging tumor capsule, thus reducing the recurrence risk.

This publication is very useful for doctors dealing with spinal tumors in their practice. The possibility of avoiding a number of serious complications and improving the efficiency of surgery necessitates adding this method to the surgical vertebrologists' practice.

O.N. Dreval' (Moscow, Russia)
The Use of Intraoperative Doppler Ultrasound in Endoscopic Transsphenoidal Surgery


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Introduction. Doppler ultrasound (DUS) has been widely used in neurosurgical practice to diagnose various cerebrovascular diseases. This technique is used in transsphenoidal surgery to identify the localization of intracranial arteries when making an approach or during tumor resection.

Materials and methods. To identify the cavernous segment of the internal carotid artery (ICA) and/or basilar artery during endoscopic transsphenoidal surgery, we used a combined device on the basis of a click line curette (Karl Storz) and a 16 MHz Doppler probe (Lassamed). The technique was used in 51 patients during both standard transsphenoidal surgery (23 cases) and transsphenoidal tumor resection through an extended approach (28 cases).

Results and discussion. Doppler ultrasound was used in different situations: to determine a trajectory of the endonasal transsphenoidal approach in the absence of the normal anatomical landmarks (16 cases), to define the limits of safe resection of a tumor located in the laterosellar region (7), and to implement an extended transsphenoidal endoscopic approach (28). Intraoperative Doppler ultrasound enabled identification of the cavernous segment of the internal carotid artery in 45 cases and the basilar artery in 2 cases; a blood vessel was not found in 4 cases. Injury to the cavernous segment of the internal carotid artery was observed only in 1 case.

Conclusion. The use of the described combined device in transsphenoidal surgery turned Doppler ultrasound into an important and useful technique for visualization of the ICA within the tumor stroma as well as in the case of the changed skull base anatomy. Its use facilitates manipulations in a deep and narrow wound and enables inspection of the entire surface of the operative field in various planes; thereby surgery becomes safer due to the possibility of maximum investigation of the operative field.

Keywords: endoscopic transsphenoidal surgery, Doppler ultrasound.

Abbreviations
DUS — Doppler ultrasound
ICA — internal carotid artery
EETA — endoscopic endonasal transsphenoidal approach
LETEA — lateral extended transsphenoidal endoscopic approach

Doppler ultrasound (DUS) is widely used at present in neurosurgical practice. It is a safe and non-invasive method of diagnosis of cerebrovascular diseases. It is used to examine blood flow parameters, to diagnose stenosis, occlusion and deformity of major arteries of the head and neck. Doppler ultrasound estimates both qualitative and quantitative indicators of blood flow in carotid and vertebral arteries [1, 2].

With the help of intraoperative DUS one can estimate hemodynamic parameters of blood flow through cerebral vessels and examine the quality of arterial aneurysm clipping (absence/presence of decreased blood flow in the carrying artery and in aneurysm after clipping) [1, 3].

The world literature includes a few publications devoted to the use of ultrasound Doppler sonography in endoscopic transsphenoidal surgery. J. Dusick et al. [4] in their work emphasize that cavernous carotid localization with the Doppler probe before dural opening can help minimize the risk of ICA injury.

Doppler ultrasonography allows detecting both safe limits for incision of the dura mater of the bottom of sella turcica and locating a blood vessel within the tumor stroma, in particular, the internal carotid artery during tumor resection from the cavernous sinus cavity [5].

We believe that since various extended endoscopic transsphenoidal approaches are used more frequently to resect a tumor located near the laterosellar region, in particular, from the cavernous sinus cavity, the application of Doppler ultrasonography in endoscopic transsphenoidal surgery is becoming increasingly important. Meanwhile, injury to ICA is one of the most serious and potentially fatal complications; hence, performance of intraoperative ultrasound imaging for avoidance of carotid artery injury is reasonable [6].

Material and Methods

We have used intraoperative Doppler sonography to locate the cavernous segment of the internal carotid artery and/or the basilar artery since 2011 during 51 cases of transsphenoidal operations. To image the operative field we use a combined device on the basis of a click line curette manufactured by Karl Storz and a 16 MHz Doppler probe manufactured by Lassamed. This device differs by a movable working part to allow inspection of vessels in various planes (Fig. 1).

During the study, the desired vessel was identified as either a red or blue strip (spectrum) in combination with the appearance of a characteristic sound of the ultrasound probe. The red spectrum indicates the direction of blood flow towards the probe and a blue one away from the
probe. In the knee of the cavernous segment of the ICA blood flows towards the probe and away from the probe, so the signal from the ICA siphon segment is characterized by appearance of both red and blue spectra (Fig. 2).

Ultrasound technique based on the Doppler effect consists in that the transducer emits a wave that bounces off moving targets (off circulating blood cells in our case) forming an echo — a reflected wave. The difference between the original and reflected wave frequencies is the Doppler shift. If the probe is located in the direction of the vessel at an angle of 90°, the ultrasound signal is absent, because the time of outgoing wave travel coincides with the time of reflected wave travel from the blood vessel to the probe. Therefore, the area of surgeon’s interest needs to be examined repeatedly at different angles.

The presence of an artery and the depth of its lying relative to a tumor or dura mater surface are displayed on ultrasound M-mode screen (Fig. 3). White dotted line and purple arrow on the right of M-Mode screen indicates the depth of spectrum lying. In this case, the boundary between the black and red/blue spectrum, which is closer to the probe, indicates the depth of the vessel (its walls) lying relative to the distal end of the probe.

Location of arteries was estimated most often in pituitary adenomas (60.8% of cases, n=31), trigeminal neuromas (15.7%, n=8), cholesteatomas (5.9%, n=3), chordomas (11.8%, n=6), meningiomas (3.9%, n=2), and low-differentiated cancer (1.9%, n=1).

Fig. 4 shows an example of using the device for intraoperative DUS.

Results

We used Doppler ultrasound to locate the ICA during standard transsphenoidal surgery, first, due to the absence of the normal anatomical landmarks in the sphenoidal sinus to determine a trajectory of the endonasal transsphenoidal approach (16 cases) and, secondly, for detection of safe limits for resection of a tumor with dense consistency located in the laterosellar region (7 cases).

When using a lateral extended transsphenoidal endoscopic approach (LETEA) the described technique allowed to detect limits of dura mater incision in a projection of the cavernous sinus to safely manipulate in the laterosellar compartment (26 cases).

The high rate of Doppler ultrasound use for timely detection of ICA in lateral extended approach (in 51.0% of cases during intraoperative Doppler sonography) is attributed to that the cavernous segment of ICA both when making an approach and during manipulations in the cavernous sinus cavity is located almost in the center of the operative field, which increases the risk of its injury.

In 2 cases (clivus meningioma) this technique was used to visualize the position of the basilar artery during tumor resection via posterior extended transsphenoidal approach.

The use of DUS allowed locating the cavernous segment of the ICA in 45 cases and locating the basilar artery in 2 cases.

In 4 cases (3 during a standard endoscopic endonasal transsphenoidal approach (EETA) and 1 with LETEA), where ultrasound examination of dura mater opening site in the projection of the cavernous sinus was performed, ICA was not detected, which indicated possibility to safely work within the visualized region.

Injuries to the ICA during appropriate and timely use of ultrasound probe were not observed. However, one injury to ICA still occurred: during an attempt to remove the neuroma of the trigeminal nerve via a lateral extended transsphenoidal endoscopic approach (1.9% of all cases where Doppler ultrasonography was used). In this case ultrasound examination of the incision region was performed in the projection of the cavernous sinus before dura mater opening in the laterosellar compartment and the artery was not found. In the safe and visualized area, dura mater was opened and the tumor was detected. Before its resection, we decided to extend dura mater incision longitudinally up to 3 mm to the area where additional detection of the carotid artery had not been conducted, and that was the cause of injury to the ICA. The intense arterial bleeding was stopped by tight tamponade of the nasal cavity with hemostatic materials (Tachocomb, hemostatic sponge, gauze turunda) followed by carotid angiography to detect the injury in the anterior knee of the cavernous segment of the right ICA. Simultaneously, endovascular occlusion of the right ICA using microcoils was performed. Postoperatively, the patient had transient paresis of the VI cranial nerve and had no negative dynamics in the rest of the neurological status.

Discussion

Injury to the internal carotid artery is one of the most serious and potentially fatal complications of transsphenoidal operations (both microscopic and endoscopic ones) [6—8].

The use of intraoperative Doppler ultrasonography allows timely detection of the artery and it prevention from injury during making an approach and tumor resection [4, 5].

Transsphenoidal operations differ by that the surgeon should always adhere to the midline; excessive deviation to a side may injure the ICA and oculomotor nerves [9].

The available anatomical landmarks (nasal septum, choanae, rostrum, the bottom of sella turcica, bone branches of the ICA, and optic carotid pouches) are commonly quite sufficient for correct-oriented and safe approach to the tumor along the midline. However, in some cases, one may fail to detect these landmarks. This can occur at repeated operations, at underdeveloped
sphenoidal sinus in children, in patients with severe infrasellar growth of tumors, in acromegaly [6].

To reduce the risk of injury to the ICA for precise determination of the middle line and position of the ICA, different electromagnetic frameless navigation systems can be used. However, in our opinion, the technique of intraoperative Doppler ultrasonography is more effective, as it allows determining the precise location of the ICA and establishing safe limits for dura mater incision of the bottom of sella turcica during standard EETA or anteroinferior wall of the cavernous sinus during LETEA. Meanwhile, when using navigation systems, with the resection of bone structures and tumor volume reduction, the initial position of the carotid artery may change.

Resection of the tumor with laterosellar spread is a challenge: they disturb the normal anatomy of the cavernous sinus, change the course of the internal carotid artery in cavernous sinus cavity, artery curves are straightened, and the artery may be displaced both to the lateral wall of the cavernous sinus and medially.

Our experience of the use of Doppler ultrasonography in tumors localized in the clivus region is still not big (only 2 cases), but in both observations DUS successfully identified the position of the basilar artery, which located on the posterior surface of clivus meningiomas and perform a safe resection of these tumors.

It is important to note that the described technique may be recommended to determine the safe limits for incision of the dura mater of the bottom of sella turcica in all cases where the operation is performed by a surgeon, having little experience of such operations (even in the presence of anatomical landmarks in the sphenoidal sinus) [4, 6, 7].
**Fig. 2.** Scheme of spectrum formation depending on the direction of sonication relative to blood flow direction (the direction of visualization is indicated by the arrows).

- **a** — 3D-reconstruction of the cavernous segment of the ICA;
- **b** — blood flow direction from the probe — blue spectrum (from the vertical portion of ICA siphon);
- **c** — blood flow direction towards the probe — red spectrum (from the horizontal portion of ICA siphon);
- **d** — blood flow direction both from the probe and towards the probe — blue and red spectra simultaneously (from the knee of ICA siphon).

**Fig. 3.** M-Mode screen.

Intraoperative visualization of blood flow in the anterior knee of the cavernous segment of the ICA based on Doppler ultrasonography data. White dotted line and purple arrow denote the distance from the middle of the artery to the probe (6.2 mm); white arrow indicates the distance from the ICA wall to the probe (4.1 mm).
Conclusions

Thus, intraoperative Doppler ultrasonography is an informative method, which provides safer transsphenoidal resection of tumors of the chiasm-sellar region and is indispensable in resection of tumors with laterosellar growth (in the projection of the cavernous sinus, the middle cranial fossa, Meckel’s cave, and pterygopalatine fossa). Applied to our case, the use of the described combined device in transsphenoidal surgery turned Doppler ultrasound into an important and useful technique for visualization of the ICA within the tumor stroma as well as the changed skull base anatomy. It facilitates the work in a narrow and deep wound creating conditions for inspecting the entire surface of the operative field in different planes. This apparatus is appropriate to apply before opening or extension of dura mater incision to minimize the risk of injury to the BCA.

Authors declare no conflict of interest.

REFERENCES

Commentary

Intraoperative contact Doppler ultrasonography is a fast, non-invasive and easy-to-repeat method to estimate blood flow in situ. The technique came into the arsenal of neurosurgeons in the early 80s of XX century, when it became possible to manufacture miniature high-frequency 1—2 mm Doppler probes. Contact Doppler ultrasound received widespread use in vascular neurosurgery, where, as shown by numerous studies, it prevents ischemic complications by estimating blood flow in the arteries after aneurysm clipping.

This work is devoted to the use of contact Doppler ultrasonography in transsphenoidal surgery, where it provides the opportunity to reveal the internal carotid artery (ICA) during endoscopic approach. Identification of the ICA wall is important when performing extended transsphenoidal approaches, repeated operations, removal of tumors with lateral growth, as well as in children with underdeveloped sphenoidal sinus lacking the normal bone anatomical landmarks. To keep the probe and change the angle of sonication the authors used a click-line device. In the majority (45 patients) of patients they have successfully managed to locate cavernous internal carotid artery and the basilar artery in 2 cases. Complications associated with diagnostics were not observed. In one case, despite the detection of the ICA, the authors experienced its injury, which was associated more with the wrong surgical tactics than with incorrect Doppler ultrasound diagnostics.

Methodology of DUS-identification of the ICA during endoscopic transsphenoidal operations reduces surgical risks and is safe and easy to use. At the same time, the authors should pay attention to that contact Doppler ultrasonography should be considered more qualitative rather than quantitative estimation of blood flow and relying on data of ICA lying depth can be quite relative. In addition, unfortunately, the authors did not compare the treatment group with the patients operated without DUS-control, which does not allow evaluating the role of technique in the prevention of complications.

V. Yu. Cherebillo (St. Petersburg, Russia)
The Algorithm of Surgical Treatment of Skull Base Tumors Invading the Craniovertebral Junction

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Burdenko Neurosurgical Institute, Moscow, Russia

Surgical treatment of skull base tumors invading the craniovertebral junction is a complex medical problem due to the high rate of adverse postoperative outcomes in these patients.

Objective. The study was aimed at optimizing surgical treatment of patients with skull base tumors invading the craniovertebral junction.

Materials and methods. A comparative analysis of 2 groups of patients was performed. The study group included 28 patients with skull base and craniovertebral junction chordomas, who underwent single-stage surgery, including posterior occipitospondylodesis and tumor resection using the transoral and combined transoral and transnasal approaches during the period from 2000 to 2015. The control group included 21 patients with the same pathology, who underwent microsurgery using transoral approach without occipitospondylodesis during the period from 1990 to 2009.

Results. Most patients in both groups were operated on at the advanced stage of the disease with severe clinical signs. The use of single-stage occipitospondylodesis and transoral skull base tumor resection significantly (compared to the control group) extends indications for surgical treatment of skull base tumors, which were previously considered unresectable, and provided better results.

Conclusion. New surgical techniques significantly improve the completeness of tumor resection, reduce the rate of postoperative complications, facilitate rehabilitation process, and improve the patient's quality of life.

Keywords: skull base surgery, craniovertebral junction, skull base chordoma, transoral approach, endoscopic transnasal approach.

Abbreviations
ICP — intracranial pressure
KS — Karnofsky score
CVJ — craniovertebral junction
CT — computer tomography
MRI — magnetic resonance imaging
OSD — occipitospondylodesis
SCT — spiral CT
TBD — total boost dose
DM — dura mater

Surgical treatment of patients with skull base tumors invading the craniovertebral junction (CVJ) is a challenging problem of modern neurosurgery, which is not fully solved yet. This is due to both complex topographic and anatomical relationship between the tumor and the surrounding structures and CVJ instability [1—4].

Surgeons often refuse to perform radical surgical treatment of patients with this disease due to the high risk of damage to the brainstem and other vital anatomical structures and rather perform palliative operations (installation of various stabilizing systems with or without decompression of the posterior fossa, biopsy followed by radiation therapy, bypass surgery) or conservative treatment (craniovertebral collar, application of Halo-apparat) [5, 20]. There are several methods of CVJ stabilization from the posterior approach: wire fixation using autogenous bone [4, 5, 8], stabilization with Magerl’s transarticular screws [6], occipitospondylodesis (OSD), and fixation with plates mounted to the lateral vertebral masses using screws, or fixation with hooked systems to the vertebral arches [7]. There is phased surgical treatment tactics, including OSD as the first stage, followed by transoral removal of the pathological process 2 to 3 weeks later as the second stage [4, 7—10].

The method of surgical treatment of skull base tumors invading the CVJ was developed at the Burdenko Neurosurgical Institute and implemented in 2000. The principle of the method lies in the simultaneous operations (under the same anesthesia), including OSD as the first stage followed by transoral (or transoral + transnasal) tumor resection [11—15].

To date, we accumulated the experience of 28 such operations in patients with skull base and CVJ chordomas, who had initial CVJ instability or were likely to develop it after radical tumor resection. According to the available world literature, this is the greatest experience of surgical...
treatment of these diseases [16, 17]. Until recently, patients with this highly complex pathology were considered to be virtually inoperable. In this study, we revised the differentiated tactics of surgical treatment, depending on the location and invasion of the process to the upper cervical segments.

Materials and methods

The study group consisted of 28 patients with skull base chordoma invading the CVJ, who were admitted to the Burdenko Neurosurgical Institute during the period from 2000 to 2015, including 11 children (5 boys and 6 girls, mean age 10 years) and 17 adults (7 males and 10 females, mean age 42 years) (Fig. 1).

In most cases, patients underwent single-stage operation, including tracheostomy, installation of OSD (in various modifications), and removal of the pathological lesion using transoral or combined (transoral and transnasal) approaches. The main stages of the operation, tumor resection in the study and control groups, were carried out by several highly skilled neurosurgeons.

In the control group, the results of treatment of 21 patients with skull base chordomas invading the CVJ have been analyzed in order to compare the effectiveness of neurosurgical treatments different from the aforementioned ones (see Fig. 1). Here was no initial CVJ instability in this group. The group consisted of 10 males (including 1 child) and 11 females, who were operated on at the Burdenko Neurosurgical Institute during the period from 1990 to 2009. Of these, 20 patients were operated through the transoral approach (including one endoscopic-assisted operation) and, in 1 case, the combination of transoral and transnasal approaches has been used. In this group of patients, OSD was not performed due to the lack of modern stabilizing systems, which obviously limited the completeness of tumor resection in many cases.

B.A. Kadashev suggested classification of pituitary tumors according to their size (1992) [18]: tumorlets, up to 15 mm, small tumors, 16 to 25 mm, medium tumors, 26 to 35 mm, large tumors, 36 to 59 mm, giant tumors, 60 mm and more. We found it possible to use this classification in our study.

Tumor sizes were distributed as follows. In the study group: giant — 64.3% (18 patients), large — 28.6% (8), medium — 7.1% (2); in the control group: giant — 52.4% (11 patients), large — 47.6% (10) (Fig. 2).

All patients underwent a comprehensive examination: neurological, neuro-ophthalmological, otoneurological, X-ray, CT, SCT, MRI, and MR angiography.

X-ray examination of the cervical spine (survey, functional) was carried out to determine the degree of destruction of skull base bone structures and C1—C2 segment, as well as CVJ instability. Additionally, transoral images of C1—C2 vertebrae were obtained. Calculation of stability of the atlanto-occipital segment was carried out by Rothman’s method (1992) [19]. Functional images of the cervical spine were used to measure Cruveilhier joint width: the distance between the posterior surface of the anterior arch of the atlas and the anterior surface of C2 odontoid process. Abnormal widening of the Cruveilhier joint (4 mm in children younger than 8 years, 2 mm in children older than 8 years and adults) was classified as instability. However, this examination was possible only in the case of relative preservation of the clival bone structures and C1 — C2 vertebrae.

In some cases, we calculated flexion-extension motions at the craniovertebral segment using S.V. Kolesov’s technique [20]. However, the study of the range of motions was impossible in the case of disseminated skull base tumors, destroying the bone structures and CVJ ligamentous apparatus, and initial instability, since removal of the cervical collar could lead to severe worsening of neurological disorders.

At the baseline, all study group patients had pronounced clinical symptoms and 13 of them were diagnosed with initial CVJ instability. In 15 cases, no CVJ instability was observed. However, in view of the dimensional characteristics of the tumor, it was predicted to occur after radical removal of the tumor, since trepanation of the anterior half-ring of C1 vertebra, odontoid process, and C2 body was planned.

![Fig. 1. Age and sex distribution of patients in the study and control groups.](image_url)
In the study group, 25 patients underwent tracheostomy before the main stages of the surgery. Nasotracheal intubation was used in 1 case (operation was carried out in 2004), and orotracheal intubation was used in 2 cases (operations were carried out in 2004 and 2005).

OSD was performed in 26 cases, including 20 cases, where hook-based stabilizing systems were used, 5 — screw-based systems, and 1 — combined hook-and-screw system. OSD systems had basically the same supporting structure and differed only in the method of fixation to bone structures (hooks or screws). The choice of stabilizing system was in all cases determined solely by the availability of a certain system provided by supplier. In 1 case, C1—C6 fusion was performed using screw system. In 1 case, OSD was performed using autogenous bone graft, which was taken from the tibia, and surgical wire (this patient was operated on in 2000). The second step included microscopic tumor resection, in some cases endoscopic-assisted. In most patients, all surgical stages were simultaneous, except for 5 patients, who underwent spinal fusion and transoral tumor resection in two stages. In 2 cases, the interval between operations was 3 and 1 years due to the fact that OSD was performed at the place of residence and then the patients applied to the Burdenko Neurosurgical Institute within a specified time. In 3 patients, the second stage of the surgery (tumor resection) was delayed by 7, 36 and 37 days due to the development of paraglossia after application of OSD.

Study group patients underwent the following surgical interventions: microsurgical transoral resection in 23 patients (endoscopic-assisted in 5 of them); combined microsurgical transoral and endoscopic transnasal resection in 5 patients. In 3 cases, optical intraoperative navigation systems were used.

Postoperative outcomes were evaluated at discharge and then on the 3rd and 6th months after the surgery. Patients were followed up for an average of 5 years.

Removed tumor volume was evaluated based on the completeness scale suggested by G. Frank and E. Pasquini [21]:

1) radical resection, when there are no signs of tumor on the control CT and/or MRI,
2) subtotal removal, when the remaining part of the tumor is less than 20% of the initial tumor size;
3) partial removal, when the remaining part of the tumor is less than 50% of the initial tumor size;
4) insufficient removal, when the remaining part of the tumor is 50% or more of its original size.

In our investigation, we used indications for the choice of a certain extracranial approach to the skull base and CVJ structures determined by J. Liu et al. [22], G.F. Dobrovol’skiy [23], and A.N. Shkarubo [24].

Indications for transoral approach include localization of the tumor in the medial and posterior parts of the clivus, C1—C2 vertebrae, and tumor invasion to the oropharynx and inferior parts of the nasopharynx. Indications for combined transoral and transnasal approaches include skull base tumors extending from the level of sella turcica to the inferior portions of the clivus and C1—C2 vertebrae, invading the nasopharynx and oropharynx.

The results of surgical treatment were evaluated based on the dynamics of clinical status, Karnofsky score, preoperative and postoperative CT, SCT, and MRI studies.

Statistical processing was performed using Matlab 2014 and Statistica 10 software. The survival rate in the study and control groups was determined using Gehan's Wilcoxon test.

Information about operation type, depending on tumor location, initial neurological status, and postoperative complications is shown in Table 1.

### Results

Obvious differences in the completeness of tumors resection in the study and control groups are shown in Fig. 3. In the study group, in 28.6% of cases (8 patients), tumor was completely removed (Fig. 10, 12, 13), in 64.3% (18) — subtotally (Fig. 11), and in 7.1% (2) — partially. Partial resection was in one case determined by extremely high density of the tumor, and
therefore there was a high risk of damage to major vessels and brainstem structures, in other cases — extremely high vascularization of chordoma, which significantly complicated the course of the operation and proceeding with tumor resection was associated with the risk of a fatal hemorrhage. In the control group of patients, completeness of resection was as follows: radical — 0, subtotal — 19% (4 cases), partial — 81% (17) (see Fig. 3).

The dynamics of clinical symptoms during the early postoperative period in the study group was as follows: improved in 75% of patients, remained unchanged in 17.8%, worsened in 7.2%; in the control group: improved in 52.4%, remained unchanged in 38.1%, and worsened in 9.5% of patients (Fig. 4).

Preoperative and postoperative dynamics of clinical symptoms in the study and control groups is shown on radar plots (Figs. 5 and 6), which clearly demonstrate that the positive dynamics prevails in the study group.

The total clinical dynamics in both groups was assessed based on conventional Karnofsky score (Fig. 7 and 8).

Baseline condition of study group patients was more severe (KS=60) compared to that in the control group patients (KS=70). After surgery, Karnofsky score was approximately equal in both groups (KS=70). Statistical studies based on χ2-test (Pearson) using Matlab 2014 software revealed statistically significant difference between the distribution of Karnofsky score value in the study and control groups.

In this study, the confidence level was 95%, significance level $p=0.05$.

The incidence of intraoperative complications (tongue edema and liquorheea) was significantly higher in the study group due to more radical tumor resection and, therefore, increased duration of operation (Table 2).

The number of postoperative complications in the study group was higher than in the control group (Table 3). This can be explained by much more radical tumor resection. There were no complications after stabilizing system installation in the study group.

All study group patients were followed up during 3.5 months to 8 years, the average follow-up period was about 2.7 years. Follow-up of study group patients revealed improvement in 8 cases, no response in 10 cases, and further augmentation of symptoms due to continued tumor growth in 10 patients. Six patients died during follow-up period. One patient died 26 days after surgery. This outcome was associated with severe edema of the brain, primarily brainstem matter (pons, medulla oblongata) with “edematic softening” foci and pulmonary edema. Five patients died within the period from 5 months to 5 years due to disease progression. Radiation therapy was recommended to all patients as soon as possible after surgery. However, it was conducted only in 20 (71%) patients within the period from 5 months to 3 years after surgery. TBD of radiation therapy was 60 to 80 Gy. In patients who underwent radiotherapy at Burdenko Neurosurgical Institute, TBD was 70 Gy or higher.

In the control group, 20 of 21 patients were followed up for 5 years. Continued tumor growth accompanied by severe bulbar disorders and tetraparesis was observed in all patients. Sixteen patients died due to continued growth with the symptoms of disease progression within the period from 6 months to 4 years. Radiation therapy was carried out only in one patient 4 months after the operation.
Table 1. Distribution of study group patients according to tumor location, phasing of the operation, and postoperative complications

<table>
<thead>
<tr>
<th>S/N</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor location</th>
<th>Preoperative neurological symptoms</th>
<th>Postoperative complications</th>
<th>Surgery type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>F</td>
<td>CLIV(m/i)+C1—C2</td>
<td>Cera, T(4), IC</td>
<td>OC</td>
<td>OSD(h) + P</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>M</td>
<td>CLIV+C1—C2+PH+NS</td>
<td>CtrA, CeraA, TES, T(4), IXs, Xs, XIIs</td>
<td>SD (1)</td>
<td>OSD(h) + P</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>F</td>
<td>CLIV+C1—C2+PH+NS</td>
<td>CtrA, Cera, TES, T(4), IXs, Xs, XIIs IC</td>
<td>—</td>
<td>OSD(h) + P N2st</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>CLIV(m/i)+C1—C2+P</td>
<td>CtrA, Cera, TES IXsd, Xsd, XIIs IC</td>
<td>—</td>
<td>OSD (ag) + P</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>M</td>
<td>CLIV(i)+C1—C2</td>
<td>CtrA, Cera, VS, TES IXs, Xs, XIIs</td>
<td>OL</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>F</td>
<td>CLIV(m/i)+C1—C2</td>
<td>CtrA, Cera, TES T(3), IXsd, Xsd IC</td>
<td>—</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>M</td>
<td>CLIV(m/i)+C1—C2</td>
<td>CtrA, Cera, TES, Vsd IXsd, Xsd, XIIsd</td>
<td>—</td>
<td>OSD (h) + P + N</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>M</td>
<td>CLIV(i)+C1—C2</td>
<td>Cera, XIIs</td>
<td>OL, OS</td>
<td>OSD (h) + P + E</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>F</td>
<td>CLIV(m/i)+C1—C2—C</td>
<td>Cera, TES</td>
<td>—</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>F</td>
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<td>CtrA, Cera, TES IXs, Xs, XIIs, IC</td>
<td>OL, IRM</td>
<td>OSD (s) P2st + E</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>M</td>
<td>CLIV(m/i)+C1—C2+PH</td>
<td>CtrA, TES, Xsd, XIIs</td>
<td>OL</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
<td>M</td>
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<td>CtrA, TES T(2)</td>
<td>OL</td>
<td>OSD (hs) + N P2st</td>
</tr>
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<td>13</td>
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<td>M</td>
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<td>OL</td>
<td>P + OSD (h)</td>
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<tr>
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<td>CLIV+C1—C2+PH+NS</td>
<td>CtrA, Cera, IXsd, Xsd, XIIsd, TES, IC</td>
<td>OL</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td>M</td>
<td>CLIV(m/i)+C1—C2+PH</td>
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<td>LR, MN</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>17</td>
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<td>F</td>
<td>CLIV(i)+C1—C2—NS</td>
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<td>OL, SD(1)</td>
<td>OSD (h) + P</td>
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<tr>
<td>18</td>
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<td>CLIV(m/i)+C1—C2</td>
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<td>OL</td>
<td>OSD (h) + P + E</td>
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<tr>
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<td>18</td>
<td>F</td>
<td>CLIV(m/i)+C1—C2+PR</td>
<td>CtrA, Cera, TES, IXsd, Xsd, XIIsd, IC</td>
<td>OL</td>
<td>OSD (h) + P</td>
</tr>
<tr>
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<td>21</td>
<td>F</td>
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<td>CtrA, IXs, XIIs, TES, IC</td>
<td>—</td>
<td>OSD (h) + P E2st</td>
</tr>
<tr>
<td>21</td>
<td>20</td>
<td>F</td>
<td>CLIV+C1—C2+PH+NS</td>
<td>CtrA, XIId, IC</td>
<td>OL</td>
<td>OSD (h) + N P2st</td>
</tr>
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<td>F</td>
<td>CLIV(i)+C1—C2</td>
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<td>—</td>
<td>OSD (h) + P</td>
</tr>
<tr>
<td>23</td>
<td>58</td>
<td>M</td>
<td>CLIV(i)+C1—C2</td>
<td>CtrA, Cera, Vs, IXs</td>
<td>—</td>
<td>OSD (h) P2st</td>
</tr>
<tr>
<td>24</td>
<td>49</td>
<td>M</td>
<td>CLIV(m/i)+C1—C2</td>
<td>CtrA, Cera, TES, IXsd, XIIsd, SD(2)</td>
<td>OD(2)</td>
<td>OSD (h) + P2st</td>
</tr>
<tr>
<td>25</td>
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<td>F</td>
<td>CLIV(i)+C1—C2</td>
<td>Cera, XIIs</td>
<td>OC</td>
<td>P + OSD (h)</td>
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<tr>
<td>26</td>
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<td>P + OSD (s)</td>
</tr>
<tr>
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<td>Cera , T(3), TES IXsd, Xsd, XIIsd, IC</td>
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<td>P + N + OSD (s)</td>
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<td>Cera , Cera, TES IXsd, XIIsd, Xd, IC</td>
<td>—</td>
<td>P + OSD (s)</td>
</tr>
</tbody>
</table>

Footnote. Location: CLIV — clivus (s — superior sections, m — medial; i — inferior); C(1) — vertebra (number); PH — oropharynx; NS — nasal sinus; PR — petrous pyramid. Preoperative neurologic symptoms: V, VII, IX, X, XII — cranial nerves, s/d — the affected side; T(4) tetraparesis (points); IC — CVJ instability; C(A) — headache; C(A) — cervical ache; TES — brainstem symptoms; HH — hypertension and hydrocephalus symptoms. Type of procedure: OSD + P — single stage OSD and transoral removal of the tumor; P — transoral removal of the tumor (OSD for M/F); P + OSD — the reverse sequence of operations; + N — transnasal resection; + E — endoscopic assistance; P2st — delayed stage of transoral resection. SD — spondylodesis C1—C6, SD type — s — screw, h — hook, sh — screw-and-hook, ag — bone autograft + wire. Postoperative complications: LR — liquorhhea n/o, SD — suture diastasis; MN — meningitis; OL — tongue edema; OC — edema of cervical soft tissues; IRM — mandibular joint stiffness; (2) — multiplicity of the surgery or complications.
operation at the place of residence, the TBD is not known.

The dynamics of 3- and 5-year survival rate in the study and control groups calculated according to Kaplan-Meier method is shown in Fig. 9.

The cumulative percentage of 3-year survival rate was 78.6% in the study group and 38% in the control group. The cumulative percentage of 5-year survival rate was 78.6% in the study group and 23.8% in the control group. Survival rates in the study and control groups were compared using Gehan's Wilcoxon test, confidence of the study was 99%, significance level \( p = 0.01 \)
Fig. 7. Preoperative Karnofsky score in the study and control groups.

Fig. 8. Postoperative Karnofsky score in the study and control groups.
### Table 2. Intraoperative complications

<table>
<thead>
<tr>
<th>Structure of complications</th>
<th>Study group, (n=28)</th>
<th>Control group, (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tracheostomy, (n=25)</td>
<td>intubation, (n=3^*)</td>
</tr>
<tr>
<td>Liquorrhea</td>
<td>8 (28.6%)</td>
<td>—</td>
</tr>
<tr>
<td>Tongue edema</td>
<td>6 (21.4%)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Footnote.* * — including 2 patients with orotracheal intubation, 1 — with transnasal intubation; ** — including 10 patients with orotracheal intubation, 2 patients with transnasal intubation;

### Table 3. Postoperative complications

<table>
<thead>
<tr>
<th>Structure of complications</th>
<th>study group, (n=28),</th>
<th>control group, (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tracheostomy, (n=25)</td>
<td>intubation, (n=3^*)</td>
</tr>
<tr>
<td>Liquorrhea</td>
<td>1 (3.57%)</td>
<td>—</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (3.57%)</td>
<td>—</td>
</tr>
<tr>
<td>Suture diastasis on the soft palate or pharynx</td>
<td>3 (10.7%)</td>
<td>—</td>
</tr>
<tr>
<td>Tongue edema</td>
<td>10 (35.7%)</td>
<td>1 (3.57%)</td>
</tr>
<tr>
<td>Edema of cervical soft tissues</td>
<td>2 (7.14%)</td>
<td>1 (3.57%)</td>
</tr>
</tbody>
</table>

*Footnote.* * — including 2 patients with orotracheal intubation, 1 — with transnasal intubation; ** — including 10 patients with orotracheal intubation, 2 patients with transnasal intubation;

**Fig. 9.** Kaplan-Meier survival plot.
(Gehan’s Wilcoxon Test (Spreadsheet 8 in the Kaplan-Meier analysis) \(WW=147.00\); \(Sum=13422\), \(Var=3371.7\); Test statistic=2.522972; \(p=0.1164\).
Fig. 10—13 shows the most demonstrative clinical cases of the surgical treatment of skull base and CVJ chordomas in the study group.

**Discussion**

In the case of invasion of skull base tumors to the superior cervical segments, radical removal of the tumor will inevitably lead to CVJ instability, which is a life threatening condition. In the control group, stabilizing operations were not carried out, mainly due to the lack of adequate systems suitable for this purpose by the time of the surgery. These operations could not provide radical resection.

Combined operations, including installation of stabilizing system (first stage of the surgery) followed by tumor resection using transoral and/or transnasal extracranial approaches (second stage of surgery) enabled more radical tumor resection. In cases where the extent of the surgery and the need for anterior resection of C2—C2 vertebrae was not known before the surgery, we used the tactics of reverse sequence of surgical phases, i.e. tumor resection as the first stage and OSD as the second stage. In these situations, safe positioning of the patient...
prior to OSD is one of the most important conditions, since it is carried out under conditions of CVJ instability resulting from tumor resection.

Tracheostomy is an important condition for this type of operations. Another types of intubation (nasotracheal or orotracheal) result in permanent restriction of “assess zone” caused by the endotracheal tube, which is located within surgeon’s field of view. The presence of an endotracheal tube as a foreign body can lead to increased number of infectious complications.

Installation of the external lumbar drainage is required for intraoperative control of ICP. In the case of intraoperative liquorrhea, lumbar catheter is removed immediately after the operation.

The surgeon should have various types of mouthgags to choose the optimal design, which will provide maximum “access zone”, even in patients with impaired mobility of the lower jaw. In the case of maxillary joint stiffness, it is necessary to use endoscopic assistance, which will significantly widen visualization and access zone (see Fig. 13).

The surgeon, who uses extracranial approaches, must be experienced in microsurgical and endoscopic techniques.

When performing trepanation of the anterior half-ring of C1 vertebra, odontoid process, and C2 vertebral

Fig. 11 (Table 1, case No 20). Patient I., 21 years. Giant skull base chordoma, invading C1—C2 vertebrae, nasopharynx, and oropharynx with initial instability of the craniovertebral junction. OSD, transoral approach. Stereotactic radiotherapy on NOVALIS linear accelerator, TBD of 70 Gy one year after the operation.

a — preoperative MRI. Severe compression of brainstem structures and superior cervical portion of the spinal cord (shown by blue arrow). Destruction of the medial and inferior portions of the clivus, C1 and C2 vertebrae. Yellow arrow indicates the direction of transoral approach; b, c — spiral CT with 3D-reconstruction shows correct position of hook-based stabilising system (the system is shown by green arrow); d, e — control MRI (d) and SCT (e) 5 months after the surgery. Subtotal tumor resection, complete decompression of brainstem structures and superior cervical spine (red arrow shows the remaining fragment of the tumor).
body, a high-speed drill with a diamond burr (diameter of 3—4 mm) and osteotribe should be used.

Our experience shows that it is advisable to use synthetic absorbable suture material characterized by medium resorption time, which is applied at the nasopharynx, oropharynx and soft palate area and does not require suture release in the future.

Positional intraoperative and postoperative tongue edema pose a big problem (see Fig. 13). The nature of this complication is not fully understood, some authors suggest [25—27] that tongue edema it may be caused by impaired venous drainage. Tongue edema occurred after OSD in 5 of 28 cases. The patients were in prone position in tight fixation system. In 3 cases, second stage of the operation was delayed by 7, 36 and 37 days due to tongue edema. Due to this fact, treatment duration increased by an average factor of 2.3. In 5 (17.9%) cases, where the extent of the surgery and the need for anterior resection of C1—C2 vertebrae was not known before the surgery, we used the tactics of reversed sequence of surgical stages, i.e. tumor resection as the first stage and OSD as the second stage.

Nutrition is the most important stage of the postoperative treatment of patients. Pastor E. et al. [4] and H. Crockard et al. [28] recommend using tube feeding in the next few days after the surgery.

In accordance with this recommendation, all our patients received enteral nutrition, table №0 (within 3—7 days). In 5 cases, parenteral nutrition was used until tongue edema relief (within 3—6 days) due to the

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**Fig. 12 (Table 1, case No 9).** Patient B., 27 years. Giant chordoma of the clivus invading the posterior surface of C1—C2 vertebrae. No initial CVJ instability. OSD, transoral approach. No radiation therapy.

a, b — preoperative MRI (A — red arrows show severe compression of the dural sac and spinal cord at the level of C1—C2—C3; b — yellow arrow indicates the direction of transoral approach); c, d — MRI (c) and SCT (d) 24 months after the operation. Radical tumor resection, complete decompression of the superior cervical spinal cord.
pronounced edema of the cervical soft tissues, tongue, and failure to install gastric tube.

Antibiotic therapy was carried out according to the standard regimen for 5—7 days.

Thus, we designed and implemented in clinical practice new surgical techniques for resection of skull base tumors invading the CVJ, which extended the indications for surgical treatment of these complex diseases that were previously considered virtually inoperable and resulted in significant improvement of the completeness of tumor resection: total from 0% to 28.6%, subtotal from 19% to 64.3%, as well as significantly improved 3- and 5-year survival of patients.

Conclusions

1. In the case of skull base tumors invading the craniovertebral junction and causing CVJ instability (initial or potential postoperative), stabilizing operation should be carried out as the first stage of the surgery followed by extracranial tumor resection.

2. Simultaneous operations (new surgical technique), including stabilizing operation and extracranial (transoral or combined transnasal and transoral) skull base tumor resection is the most adequate tactics of surgical treatment of this complex group of patients.

3. The use of new surgical techniques in the surgery of skull base and craniovertebral junction tumors results in increased completeness of tumor resection: proportion of radical resection increased from 0% in the control group to 28.6% in the study group, subtotal — from 19% in the control group to 64.3% in the study group.

4. The use of new surgical techniques lead to increased 3-year survival from 38% in the control group to 78.6% in the study group, and 5-year survival from 23.8% in the control group to 78.6% in the study group.

5. These operations require coordinated teamwork of neurosurgeons, anesthesiologists, and intensive care doctors at all stages of treatment and should be performed in highly specialized healthcare facilities. Neurosurgeons must be perfect in both microsurgical and endoscopic techniques for resection of these tumors, whose location complicated the operation.

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Authors declare no conflict of interest.
REFERENCES


Commentary

This report is a result of a 15-year-long research and hard work aimed at solving the issue of the strategy of surgical treatment of skull base tumors invading the craniovertebral junction. It should be noted that this is a neurosurgical pathology, which can be surgically treated only by a few highly skilled neurosurgeons in some worldwide leading neurosurgical institutions.

The study involves 49 patients with severe pathology, 28 of them comprise the study group, where the authors performed occipitopetrosyndesmosis as the first stage and transoral or, when indicated, transnasal tumor resection as the second stage. In the control group, extracranial resection of skull base tumors was performed without occipitopetrosyndesmosis.

Clinical, radiographic, and follow-up studies convincingly shown that single-stage stabilization and tumor resection can significantly improve the completeness of resection, reduce postoperative complications, facilitate recovery, and improve the quality of life of patients.

I have no principal critical remarks to the study. The only thing to note is that there is no need to describe the pituitary tumors classification was used in this study.

The authors used various stabilizing systems for occipitopetrosyndesmosis. I would like to clarify whether the choice was based on indications or not. “Conclusion” or “Summary” would be more appropriate title for the section titled “Discussion” and this is the last possible remark.

The work is highly relevant and it is of great scientific and practical interest.

O. N. Drevael' (Moscow, Russia)
Overall Survival and Intracranial Relapses in Patients with Brain Metastases after Gamma Knife Radiosurgery Alone

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1Burdenko Neurosurgical Institute, Moscow, Russia; 2Gamma Knife Center, Moscow, Russia

Purpose. The study purpose was to evaluate the impact of gamma knife radiosurgery (GKRS) alone on the overall survival and intracranial recurrence rates in brain metastasis patients.

Material and methods. Treatment outcomes in 502 patients (211 males and 291 females) with 2,782 brain metastases (BMs) were retrospectively reviewed. Most of the patients (n=142; 28.2%) were diagnosed with breast cancer. Multiple BMs were detected in 259 patients (51.6%). The median total BM volume was 5.9 cm³ (range, 0.09—44.5 cm³), and the median BM number was 4 (range, 1—36). The mean marginal radiation dose was 21 Gy (range, 15—24 Gy). The mean follow-up period was 10.6 months (range, 0.2—47.2 months).

Results. The overall survival rate at 12 and 24 months was 37.6 and 19.1%, respectively. The median overall survival after GKRS was 8.6 months (95% confidence interval (CI), 7.0—10.0). Local control of metastatic lesions was achieved in 78.8% of patients. The median local recurrence-free survival after radiosurgery was 6.8 months. The development of new (distant) metastases was observed in 49.5% of patients. The median distant metastasis-free time was 8.8 months. The prognostic factors for better survival are as follows: the Karnofsky performance score (KPS) of >80 (HR 0.3935; 95% CI, 0.2429—0.6376; p=0.0002), BM number of <3 (HR 0.6138; 95% CI, 0.3993—0.9943; p=0.0269), and BMs of breast and lung cancers (HR, 0.5442; 95% CI, 0.3642—0.8071; p=0.0027). In the case of intracranial metastasis recurrence, repeated radiosurgery provides the median overall survival of 19.6 months versus 9.6 months in patients without radiosurgery (HR, 0.4026; 95% CI, 0.2381—0.6809).

Conclusions. Radiosurgical treatment of patients with multiple BMs provides the median overall survival of 8.6 months. The predictors of better survival include a good functional status, non-extensive metastasis of the brain, and radiosensitive morphology of the primary tumor. Repeated radiosurgical treatment for intracranial recurrences provides longer overall survival compared to that in patients without repeated radiosurgical treatment.

Keywords: radiosurgery, brain metastases, whole brain radiotherapy, gamma knife.

Abbreviations
KPS — Karnofsky performance score
CRC — colorectal cancer
CT perfusion — computed tomography perfusion
BM — brain metastasis
MRI — magnetic resonance imaging
NSCLC — non-small cell lung cancer
WBRT — whole brain radiotherapy
PET — positron emission tomography
BC — breast cancer
RCC — renal cell carcinoma
RS — radiosurgery

Symptomatic brain metastases (BMs) occur in 8—10% of cancer patients. The rate of BM diagnosis will likely grow because improvements in drug therapy increase overall survival of oncological patients [1—3].

The course of disease is aggressive in most patients with BMs. Almost 80% of patients have multiple (>3) BMs at the time of diagnosis, and approximately 10—15% of metastatic lesions are localized in the deep parts of the brain. These patients often present with neurological and cognitive dysfunction. Therefore, improvement in the performance status and quality of life is as important as an increase in overall survival. The prognosis for BM patients remains poor; the median overall survival, if untreated, is less than 1 month [4, 5].

The efficacy of chemotherapy in these patients is low due to limited penetration of most drugs through the blood-brain barrier. Surgery and whole brain radiotherapy (WBRT) still remain the major techniques for treatment of BM patient [6, 7]. Usually, surgical treatment rapidly decreases clinical signs of the mass effect and enables histological and immunohistochemical studies of the tumor [6, 8]. However, surgery is not always possible, especially in patients with a poor performance status (Karnofsky performance score (KPS) ≤70), multiple BMs, or metastases in the eloquent brain areas [9, 10].

WBRT is performed as monotherapy or adjuvant therapy after surgical treatment or radiosurgery (RS).
WBRT provides control of both apparent BMs and micrometastases [11, 12]. On average, survival after WBRT alone is approximately 4 months and 6—9 months after combined treatment (surgical resection and WBRT) [13—15].

Radiosurgery provides selective irradiation of small intracranial lesions per one session, with minimal exposure of surrounding normal brain tissues [16—18]. Radiosurgery has become the method of choice for treatment of single and multiple BMs due to good local tumor control and a low complication rate [17, 19].

Radiosurgery has the following advantages over surgical treatment and WBRT:

• treatment of BMs localized in the deep parts or functional areas of the brain;
• outpatient treatment option;
• treatment of multiple (>3) BMs;
• preservation of cognitive functions [20];
• re-treatment option.

In the present study, we analyzed treatment outcomes in BM patients treated by gamma knife radiosurgery (GKRS) alone.

Material and Methods

Patient characteristics
A retrospective analysis included patients who received radiosurgical treatment at the Gamma Knife Center in the period from 2010 to 2014. Given the study purposes, patients who received WBRT or surgical treatment before or after RS were excluded from the analysis. The study group consisted of 502 patients: 211 males and 291 females, aged 22 to 89 years (mean age, 56 years) (Table 1).

It should be noted that KPS of ≤70 was in 152 (33.1%) patients before RS. BMs of radiosensitive tumors (BC and NSCLC) were detected in 269 (53.6%) patients. At the time of topometric magnetic resonance imaging (MRI) before RS, 101 (20.1%) patients had 1 BM, and 88 (17.5%) patients had more than 10 BMs. Totally, 2,782 BMs were treated by RS. The analysis also included patients who received repeated RS for local relapses or new (distant) metastases.

After RS, all patients underwent MRI every 3 months. Local tumor control was defined as no increase (>25%) in size of an exposed metastatic lesion based on MRI data. CT perfusion or PET with fluorocholine was used to differentiate relapses from radiation necrosis.

Radiosurgical technique
All patients underwent fixation of a stereotactic frame under local anesthesia, followed by topometric MRI of the brain. We used high-resolution MRI with a scanning pitch of 1 mm. GammaPlan software (version 10.1) was used for planning purposes. A radiosurgery target was defined as the area of abnormal contrast agent uptake. The mean marginal radiation dose in most cases was 21 Gy (range, 15—24 Gy) at the 50% isodose line.

Statistical methods
The main analyzed clinical factors were as follows: the age, KPS, BM number, total BM volume, maximum BM volume, time from disease onset to BM development, and primary tumor morphology. Clinical events subjected to the analysis were as follows:

• overall survival: the time from RS therapy for initially diagnosed BMs to the latest examination or death.

Intracranial relapses:

• local relapse-free survival: the time from RS therapy to the time of relapse in the exposed site;
• distant metastasis-free survival: the time from RS therapy to the time of new (distant) metastasis detection outside the exposure area.

Overall survival was analyzed using the Kaplan-Meier method; group differences were calculated using the log-rank test. The data of patients survived at the time of the latest examination were considered censored.

A proportional hazards regression model was used to determine the hazard ratio (HR) for potential prognostic factors influencing overall survival, local relapse, and development of distant metastases.

All statistical analyses were performed using MedCalc version 15 software; p<0.05 was considered as statistically significant.

Overall outcomes of radiosurgery
By the end of analysis, 57 (23.1%) patients were followed-up, and 189 (76.8%) patients died. The mean follow-up period was 10.6 months (range, 0.2—47.2 months). The median overall survival was 8.6 months (95% CI, 7.0—10.0). The overall survival rate at 12 and 24 months was 37.6 and 19.1%, respectively.

The development of new (distant) metastases occurred in 164 (49.5%) patients. The median distant metastasis-free time was 8.8 months (95% CI, 7.3—10.6). The distant metastasis-free survival rate at 12 and 24 months was 38.9 and 24.3%, respectively.

Local relapses occurred in 72 (22.2%) patients. Local relapse occurred in 84.7% of patients of this group within first 12 months and in 15.3% of the patients in the period from 12 to 24 months. The median local relapse-free time was 6.9 months (95% CI, 5.9—8.2).

Analysis of clinical factors affecting overall survival
We assessed the effect of clinical factors (age, time from the tumor diagnosis to BMs, KPS, BM number, maximum BM volume, BM morphology) on overall survival.

Primary tumor morphology
In the analysis, patients with radiosensitive tumors were predominant: breast adenocarcinoma, lung
adenocarcinoma, and squamous cell lung carcinoma were in 269 (53.6%) patients (Table 1).

The median survival of patients in groups of radiosensitive (BC, NSCLC) and radioresistant (RCC, CRC, melanoma) BMs was 11.6 and 7.2 months, respectively (Fig. 1). The overall survival rate of patients at 12 and 24 months was 49.8 and 32.5%, respectively, in the radiosensitive tumor group versus 26.2 and 7.2%, respectively, in the radioresistant tumor group.

Thus, the survival of patients in the radiosensitive tumor group was higher than that in patients with radioresistant tumors (HR, 0.5816; 95% CI, 0.4361–0.7756; \( p=0.0027 \)). This fact reflects high sensitivity of BC and NSCLC to ionizing radiation and their low radiation damage repair capacity.

Table 1. Characteristics of study patients

<table>
<thead>
<tr>
<th>Total of patients (( n=502 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males 211</td>
</tr>
<tr>
<td>Females 291</td>
</tr>
<tr>
<td>Mean age, years 56 (22 to 89)</td>
</tr>
<tr>
<td>&gt;60 years 194</td>
</tr>
<tr>
<td>≤60 years 308</td>
</tr>
<tr>
<td>Total number of BMs treated by radiosurgery 2782</td>
</tr>
<tr>
<td>Mean number of BMs per patient 5</td>
</tr>
<tr>
<td>BMs ≤3 243</td>
</tr>
<tr>
<td>BMs &gt;3 259</td>
</tr>
<tr>
<td>Total BM volume, cm^3 Median volume, 5.9 cm^3</td>
</tr>
<tr>
<td>BMs ≤5 cm^3 225</td>
</tr>
<tr>
<td>BMs &gt;5 cm^3 275</td>
</tr>
<tr>
<td>N/A 2</td>
</tr>
<tr>
<td>Karnofsky performance score (KPS):</td>
</tr>
<tr>
<td>≤70 152</td>
</tr>
<tr>
<td>&gt;80 307</td>
</tr>
<tr>
<td>N/A 43</td>
</tr>
<tr>
<td>Time to BM development:</td>
</tr>
<tr>
<td>≤12 months 141</td>
</tr>
<tr>
<td>&gt;12 months 160</td>
</tr>
<tr>
<td>N/A 201</td>
</tr>
<tr>
<td>Maximum BM volume:</td>
</tr>
<tr>
<td>≤4 cm^3 244</td>
</tr>
<tr>
<td>&gt;4 cm^3 251</td>
</tr>
<tr>
<td>N/A 7</td>
</tr>
<tr>
<td>Radiosurgery (( n=502 ))</td>
</tr>
<tr>
<td>1 session 386</td>
</tr>
<tr>
<td>2 sessions 91</td>
</tr>
<tr>
<td>3 sessions 18</td>
</tr>
<tr>
<td>4 sessions 6</td>
</tr>
<tr>
<td>5 sessions 1</td>
</tr>
<tr>
<td>Morphological diagnosis (( n=502 ))</td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC) 127</td>
</tr>
<tr>
<td>Breast cancer (BC) 142</td>
</tr>
<tr>
<td>Renal cell carcinoma (RCC) 93</td>
</tr>
<tr>
<td>Colorectal cancer (CRC) 27</td>
</tr>
<tr>
<td>Melanoma 113</td>
</tr>
<tr>
<td>Radiosensitive tumors (NSCLC, BC) 269</td>
</tr>
<tr>
<td>Radioresistant tumors (RCC, CRC, melanoma) 233</td>
</tr>
</tbody>
</table>

Performance status (Karnofsky scale)
In general, patients with KPS ≥80 prevailed in groups (\( n=307, \) 62.0%). The median survival of patients in groups with KPS ≥80 and KPS ≤70 was 11.6 and 4.1 months, respectively (Fig. 2). The overall survival rate of patients at 12 and 24 months was 48.8 and 25.6% in the group with KPS ≥80 versus 16.9% and 0 in the group with KPS ≤70, respectively.

Thus, the survival of patients in the group with a good performance status (KPS ≥80) was higher than that in the group with KPS ≤70 (HR, 0.4428; 95% CI, 0.2959–0.6624; \( p<0.0001 \)).

BM number
Patients with multiple (>3) BMs slightly prevailed in the study group (\( n=259, \) 51.5%). The median survival in groups with few (≤3) and multiple (>3) BMs was 12.5 and 6.4 months, respectively (Fig. 3). The overall survival rate of patients at 12 and 24 months was 50.6 and 13.6%, respectively, in patients with multiple BMs.

Thus, the survival of patients with few BMs was higher than that of patients with multiple BMs (HR, 0.6344; 95% CI, 0.4764–0.8447; \( p=0.0017 \)).

Total BM volume
Patients with a total BM volume of >5 cm^3 prevailed in the study population (\( n=275, \) 55.0%). The median survival of patients in groups with a total BM volume of ≤5 cm^3 and >5 cm^3 was 13.3 and 7.7 months, respectively.

The overall survival rate of patients in the group with a total BM volume of ≤5 cm^3 at 12 and 24 months was 51.1 and 27%, respectively, versus 26.6 and 14.3%, respectively, in the group with a total BM volume of >5 cm^3.

Thus, the survival of patients in the group with a total BM volume of ≤5 cm^3 was higher than that in the group with a total BM volume of >5 cm^3 (HR, 0.7328; 95% CI, 0.5506–0.9754; \( p=0.0317 \)).

The results of regression analysis (Cox) are presented in Table 2. The best survival occurred in patients with BMs of radiosensitive tumors, a good performance status (KPS ≥80), few (≤3) BMs, and a total BM volume of ≤5 cm^3.

The multivariate analysis reveals that only BMs of radiosensitive tumors, a small BM number, and a good performance status are factors of better overall survival of BM patients (Table 2).

Analysis of clinical factors affecting local relapse
Local relapses were detected in 72 (22.2%) of 324 patients who underwent RS and for whom the database had records on the presence/absence of local relapses. In the univariate analysis, statistically significant factors of local relapse were as follows: the total BM volume (HR, 0.4996; 95% CI, 0.3145–0.7937; \( p=0.0033 \)), maximum BM volume (HR, 0.3731; 95% CI, 0.2335–0.5963;
In the multivariate analysis, a lower rate of local relapses was associated with a maximum BM volume of less than 4 cm³ (HR, 0.203; 95% CI, 0.0751—0.5486; \( p < 0.0018 \)) and BMs of radiosensitive tumors (HR, 0.359; 95% CI, 0.1920—0.6173; \( p < 0.0114 \)).

In the multivariate analysis, a lower rate of local relapses was associated with a maximum BM volume of less than 4 cm³ (HR, 0.203; 95% CI, 0.0751—0.5486; \( p < 0.0018 \)) and BMs of radiosensitive tumors (HR, 0.359; 95% CI, 0.1920—0.6173; \( p < 0.0114 \)).

**Analysis of clinical factors affecting development of distant metastases**

The development of distant metastases was detected in 164 (49.5%) patients. In the univariate analysis, statistically significant prognostic factors for low risk of distant metastases were as follows: the BM number ≤3 (HR, 0.4463; 95% CI, 0.3267—0.6096; \( p < 0.0001 \)), KPS≥80 (HR, 0.3731; 95% CI, 0.4334—0.9465; \( p < 0.0097 \)), and BMs of radiosensitive tumors (HR, 0.6092; 95% CI 0.4409—0.8417; \( p < 0.0012 \)).

In the multivariate analysis, a lower rate of distant BMs was associated only with a small BM number (HR, 0.39; 95% CI, 0.2497—0.6087; \( p < 0.0001 \)).

**Effect of repeated radiosurgery for intracranial relapses on overall survival**

Intracranial relapses were detected in 197 patients of the whole study group. Local relapses or distant metastases alone occurred in 31 and 125 patients, respectively. Concomitant local relapses and distant metastases were in 41 patients. Of the total number of patients with intracranial relapses, 98 patients with a first intracranial relapse underwent repeated RS. Withholding repeated RS in the remaining 99 patients was partially associated with either contraindications for radiosurgery (disseminated BMs or a low performance status) or application of another treatment (surgery, WBRT, chemotherapy). Figure 4 presents median overall survivals for different treatment options for intracranial relapses.

The median overall survival in patients with intracranial relapses who underwent repeated RS was 19.6 (95% CI, 16.1—26.9) months compared to 9.6 (95% CI, 7.6—13.3) months in patients without radiosurgery. The overall survival rate in patients with intracranial relapses at 12 and 24 months was 34.9 and 14.7%, respectively, in a group of single radiosurgery versus 73.5 and 38.4%, respectively, in patients with repeated RS.

Thus, increased survival and reduced risk of death (HR, 0.4026; 95% CI, 0.2381—0.6809) were observed in patients with repeated RS for intracranial relapses.

**Discussion**

The current single-center retrospective study confirms the data showing the efficacy of radiosurgery alone in treatment of BM patients [18].

In the whole study group, the median overall survival after RS was 8.6 months, exceeded the median survival of patients with a good performance status and a single BM after WBRT alone, and was close to the median survival of patients with single metastases who underwent modern surgical treatments and WBRT [15, 21].

The data of published studies demonstrate the advantage of RS treatment in prolongation of survival for
patients with a good baseline performance status (KPS≥80). The present study demonstrates higher median overall survival in patients with a good performance status compared to that in patients with KPS ≤70.

Many potential prognostic factors and prognostic systems for overall survival of BM patients have been well investigated. However, there are debatable opinions on prognostic factors, especially when different treatments are used: surgery, WBRT, radiosurgery, or combined treatment [10, 21—24].

A set of prognostic factors significantly varies in different studies. The main prognostic factors for better survival include age, a good performance status (KPS≥80), control of the primary site, and the absence of extracranial metastases. In contrast, the number and/
or total volume of BMs may have a smaller effect on overall survival.

Our findings are consistent with the data indicating no relationship between RS outcomes and age [25, 26]. However, some authors reported a difference in survival among different age groups [10, 27].

Furthermore, our study does not confirm a better overall survival of females after RS demonstrated in a study by T. Serizawa et al. [18] and is fully consistent with the data of F. Lagerwaard et al. [13] that overall survival is not affected by gender [28].

It should be noted that BC and BM female patients with c-erbB2 overexpression have better survival. Consequently, the prevalence of BC female patients in a study may unreasonably lead to a conclusion about longer survival of patients in the whole group.

Our findings are completely consistent with the data on better survival of patients with few (<3) BMs [21, 27]. Many reports have demonstrated that multiple (>3) metastatic lesions are usually associated with a shorter overall survival [10, 29]. For this reason, most radiosurgery centers limit the indications for radiosurgery to patients with less than ≤4—5 BMs, followed by WBRT. However, using WBRT in this situation is not affected by gender [28].

Similarly, B. Karlsson et al. [27] did not find significant differences in overall survival among patients with 2, 3—4, 5—8, and more than 8 BMs after RS therapy. Many researchers emphasize that control of systemic disease is much more important than the number of BMs for survival of patients.

There are different opinions regarding the primary tumor morphology as a prognostic factor for overall survival [10, 24]. In the present study, the morphology of BMs is an important prognostic factor for overall survival. Patients with BMs of radiosensitive tumors (BC and NSCLC) have better survival than patients with radioresistant BM morphology (melanoma, RCC, CRC). Some studies have not found any effect of the BM morphology on survival after exclusion of BC patients because these patients have better overall survival. In the present study, exclusion of BC female patients from the analysis retained a statistical difference in the overall survival (p=0.0046) in patients with different BM morphologies: the poorest median overall survival (5.2 months) was in melanoma patients, and the best median overall survival (9.9 months) was in NSCLC patients.

Some studies demonstrated that the total BM volume, volume of the maximum lesion, and marginal dose may correlate with the overall survival and local control of an irradiated lesion [30]. According to the univariate analysis, a total BM volume of less than 5 cm³ was associated with a longer median survival, though this fact was not confirmed by the multivariate analysis (Table 2).

The regression analysis (Cox) results confirm the fact that a good performance status (KPS≥80), few (<3) BMs, and radiosensitive histology of the primary tumor (NSCLC, BC) are significant predictors for improved survival of BM patients (Table 2). Table 2 shows the results of major studies on RS treatment outcomes in BM patients.

Almost all studies were conducted in patients with few (<3) BMs. In these patients, the radiosurgery outcomes in our study are almost identical to the data reported by H. Aoyama et al. [31] and T. Serizawa et al. [18].

However, a relatively high rate of new (distant) metastases was observed in the present study, especially in comparison with the data of M. Yamamoto et al. [30]. This fact is explained by prospective nature of the Yamamoto’s study and limited inclusion of patients with a low performance status and progressive systemic

### Table 2. The results of regression analysis of clinical factors influencing overall survival of BM patients

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI for HR</td>
</tr>
<tr>
<td>Age (&lt;60 years / ≥60 years)</td>
<td>1.0522</td>
<td>0.7886—1.4039</td>
</tr>
<tr>
<td>Time from disease onset to BM development (&lt;12 months / ≥12 months)</td>
<td>1.1072</td>
<td>0.7576—1.6183</td>
</tr>
<tr>
<td>Karnofsky performance score (&gt;80 / ≤70)</td>
<td>0.4428</td>
<td>0.2959—0.6624</td>
</tr>
<tr>
<td>BM number (&lt;3 / ≥3)</td>
<td>0.6344</td>
<td>0.4764—0.8447</td>
</tr>
<tr>
<td>Total BM volume (&lt;5 cm³ / ≥5 cm³)</td>
<td>0.7328</td>
<td>0.5506—0.9754</td>
</tr>
<tr>
<td>Maximum BM volume (&lt;4 cm³ / &gt;4 cm³)</td>
<td>0.8593</td>
<td>0.6444—1.1459</td>
</tr>
<tr>
<td>BM morphology (BC, NSCLC/ melanoma, CRC, RCC)</td>
<td>0.5816</td>
<td>0.4361—0.7756</td>
</tr>
</tbody>
</table>
Fig. 4. Overall survival of patients with developed intracranial relapses, depending on the number of RS sessions.

### Table 3. The results of pivotal studies of radiosurgery outcomes in BM patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of BMs</th>
<th>Radiation dose</th>
<th>Local control at 12 months, %</th>
<th>Distant metastases at 12 months, %</th>
<th>Median overall survival</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews, 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBRT</td>
<td>164</td>
<td>1–3</td>
<td>37.5 Gy/3 w</td>
<td>71</td>
<td>30</td>
<td>4.9</td>
<td>0.0393</td>
</tr>
<tr>
<td>RS+WBRT</td>
<td>167</td>
<td>1–3</td>
<td>15—24 Gy</td>
<td>82</td>
<td>25</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Aoyama, 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>67</td>
<td>1–4</td>
<td>18–25 Gy</td>
<td>72.5</td>
<td>76.4</td>
<td>8.0</td>
<td>0.42</td>
</tr>
<tr>
<td>RS+WBRT</td>
<td>65</td>
<td>1–4</td>
<td>30 Gy/10 fr</td>
<td>88.7</td>
<td>46.8</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Muacevic, 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery+WBRT</td>
<td>83</td>
<td>&lt;2 cm in diameter</td>
<td>40 Gy/4 w</td>
<td>82</td>
<td>N/A</td>
<td>9.5</td>
<td>0.8</td>
</tr>
<tr>
<td>RS</td>
<td>31</td>
<td>14–27 Gy</td>
<td>96.8</td>
<td>N/A</td>
<td>10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serizawa, 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>778</td>
<td>1–3</td>
<td>13.5–30</td>
<td>77.9–98.4</td>
<td>45.7</td>
<td>26.4 (RPA 1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.4 (RPA 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.6 (RPA 3)</td>
<td></td>
</tr>
<tr>
<td>Kocher, 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS+WBRT</td>
<td>99</td>
<td>1–3</td>
<td>20 Gy</td>
<td>81</td>
<td>48</td>
<td>10.9 (with WBRT)</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>Surgery+WBRT</td>
<td>81</td>
<td>1–3</td>
<td>30 Gy/10 fr</td>
<td>73</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>100</td>
<td>1–3</td>
<td>20 Gy</td>
<td>69</td>
<td>33</td>
<td>10.7 (without WBRT)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>79</td>
<td>1–3</td>
<td>41</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamamoto, 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>548</td>
<td>1–4</td>
<td>10–2 Gy</td>
<td>91.5</td>
<td>30.3</td>
<td>7.9</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td></td>
<td>548</td>
<td>&gt;5</td>
<td>92.6</td>
<td>29.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma Knife Center, Moscow, 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS¹</td>
<td>502</td>
<td>Without restrictions</td>
<td>15—24 Gy</td>
<td>78.8</td>
<td>60.4</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>RS²</td>
<td>187</td>
<td>1–3</td>
<td>79.2</td>
<td>45.5</td>
<td></td>
<td>9.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>194</td>
<td>&gt;3</td>
<td>74.1</td>
<td>68.7</td>
<td></td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

Footnote. RS¹ — radiosurgery outcomes in the whole group, including patients with repeated RS. RS² — outcomes in patients with single RS.
disease, which probably reduces the prognostic value of the BM number with respect to overall survival and development of distant metastases. The present study is retrospective and includes patients with a low performance status and multiple extracranial lesions. In this situation, the number of BMs is an important prognostic factor for both overall survival and development of distant metastases in a study population. However, this concept needs to be examined in further prospective studies.

If radiosurgery alone is a sufficient treatment option?

An article by A. Muacevic et al. [9] reports the results of a randomized controlled multicenter study that evaluated the effect of RS alone and the effect of surgery combined with WBRT in patients with single resectable BMs. Both groups were similar in local control and overall survival. However, the rate of distant metastases was significantly higher in the group of RS alone. Some studies reported an increased risk of new (distant) metastases in patients treated with RS alone [31, 32]. The data of our study confirm the fact that patients with three or more BMs have a higher risk of distant BMs.

These conclusions lead to at least two questions.

1. If RS alone is an effective and appropriate treatment for BM patients?
2. If combined treatment (RS with simultaneous or delayed WBRT for intracranial relapses) improves local control of BMs, avoids distant metastases, and increases overall survival?

The design of early studies was aimed at comparing WBRT and combined treatment (RS+WBRT). In 1999, D. Kondziolka [28] demonstrated that combination of WBRT and radiosurgery significantly improved local control of brain metastases compared to WBRT alone. The study was stopped prematurely due to 100% of local relapses in a WBRT group and 8% of local relapses in a combined treatment group. However, the overall survival was identical in both groups.

These data were in general confirmed by a multicenter randomized study RTOG 95-08 that revealed no statistical difference in overall survival between a combined treatment group (6.7 months) and a WBRT group (5.7 months). However, an analysis of subgroups found a small advantage of the combined treatment group (6.5 months) over the WBRT group (4.9 months; \( p=0.04 \)) in overall survival of patients with a single metastasis. These findings were also controversial due to the fact that 19% of patients in the combined treatment group did not receive RS, and 15% of patients in the WBRT group eventually underwent RS [33].

To find answers to the above questions, the study design was changed, focusing on comparison of radiosurgery and combined treatment (RS+WBRT). The study design modification was mainly related to a high rate of cognitive disorders in the WBRT group.

The data of a randomized controlled study conducted by H. Aoyama et al. [31] demonstrated that radiosurgery and WBRT reduced the rate of intracranial relapses, but this was not accompanied by an increase in overall survival.

In 2010, Chirato demonstrated that the general condition of patients and local control of BMs were better in the combined treatment group, but adding WBRT did not lead to an increase in overall survival.

A randomized controlled multicenter phase III study EORTC 22952-26001 confirmed the data on a higher rate of intracranial relapses after radiosurgery without WBRT in patients with few \((\leq 3)\) BMs. Although the risk of intracranial relapses was significantly reduced in the WBRT group, it was not possible to increase the overall survival and duration of a good performance status [35, 36].

Obviously, control of BMs after RS and WBRT is not associated with better overall survival [10, 27, 35]. This fact is probably related to a low efficacy of WBRT in terms of prevention of distant metastases and/or to a short duration of the effect, which are insufficient to increase the survival rate. Furthermore, WBRT was performed only once, which raises a question about treatment options for intracranial relapses after WBRT.

Radiosurgery has no restrictions typical of WBRT: repeated RS in the case of intracranial relapses enables achieving high local control at lower toxicity and better overall survival [25, 27].

Our findings confirmed the fact of better survival of patients who underwent repeated RS for intracranial relapses compared to patients without RS. Therefore, strict follow-up after RS, regular MRI for early detection of intracranial relapses, and subsequent radiosurgery are the optimal diagnostic algorithm [37].

**Conclusions**

Our findings demonstrated the efficacy of RS in the whole group of BM patients.

Local control of BMs was achieved in 77.8% of patients with the median overall survival of 8.6 months and overall survival at 12 and 24 months 37.6 and 19.1%, respectively.

The largest increase in the median overall survival is achieved in patients with a good performance status, few metastatic brain lesions, and BMs of radiosensitive tumors.

It seems to be doubtful to perform WBRT in patients with a good performance status and few BMs; clarification of the indications for WBRT in patients with multiple BMs is required.

Repeated RS ensures better survival indicators compared to other treatments for intracranial relapses.

Authors declare no conflict of interest.
The frequency of brain metastases is steadily increasing. According to conservative estimates, 8—10% of cancer patients develop symptomatic brain metastases. In recent years, systemic drug therapy has played an important role in the treatment of patients with brain metastases. Contemporary drug therapy for brain metastases includes both standard chemotherapy regimens and target therapy.

Most antineoplastic drugs have a limited ability to penetrate the blood-brain barrier due to their low lipophilicity and/or high molecular weight. Surgical and radiosurgical treatment should be considered as an optimal treatment option for patients with brain metastases.

In this paper, the authors analyzed outcomes in 502 patients who underwent stereotactic treatment for brain metastases using a Gamma Knife machine. Of great importance is a high median survival of 8.8 months in this group of patients, with local relapses in 22% of patients and new (distant) metastases in 50% of patients. The data are consistent with the parameters reported by large international radiosurgery centers. A distinctive feature of this work is establishment of the prognosis for the main clinical factors: overall survival and development of distant metastases and local relapses.

Unfortunately, the work lacks the data on the effect of systemic drug therapy and generalization of extracranial disease on overall survival. There is no data on the distribution of patients according to the GPA scale and RPA classes. Undoubtedly, these data would increase the analytical value of this work.

In conclusion, it should be noted that stereotactic radiosurgery opens up new opportunities in treatment of patients with brain metastases.

A. K. Bekyashev (Moscow, Russia)

 Commentary

This article presents a retrospective analysis of overall survival and intracranial relapses in a group of 502 patients with solid tumor brain metastases who underwent radiosurgery using a Gamma Knife machine at the Gamma Knife Center of the Burdenko Neurosurgical Institute. The article is also dedicated to identification of prognostic factors for survival and relapse.

The merit of the study is that it analyzes the efficacy of radiosurgery in a large representative group of patients with brain metastases treated using the Gamma Knife machine. On the one hand, similar studies allow evaluating the efficacy of existing treatment experience and serve the landmark for analysis of new treatment outcomes in this complex group of patients in the future; on the other hand, these studies enable evaluating potential disadvantages of used treatment approaches and proposing new treatment algorithms.

The median overall survival in the whole group was 8.6 months after radiosurgical treatment. This is somewhat higher than that in large series of observations. For example, J. Barnholtz-Sloan et al. (2012) analyzed the data of seven randomized studies with a total of 2,350 patients and found the median survival of 4.7 months. At the same time, H. Aoyama (included in the reference list) reported a one-year survival rate of 81% for hypofractionated radiotherapy in patients with brain metastases. In Discussion, the authors indicate that the median survival was 9.9 months in patients with non-small cell lung cancer and only 5.2 months in patients with melanoma. In general, it is clear that there is no a single disease called “brain metastasis”. However, these different survival indicators need to be analyzed not “in general”, but differentiated depending not only on the primary tumor site (breast cancer, lung cancer, melanoma, etc.) but also on the histological diagnosis and molecular genetic features.

Furthermore, we would like to enter into a discussion with the authors regarding several issues.

This is not a pioneer work in our country; e.g. S. R. Il’yalov, a co-author, is the author of papers and a PhD thesis on a similar subject. So, it is surprising that the study lacks either references to his papers or attempts to compare the present data with the results of similar studies performed at the same center. Another critical weakness of the work is an incomplete description of the data collection methodology. For example, the authors report mean metastasis volumes, but do not specify a method of their estimation. The section Radiosurgical technique seems to be quite brief; it just lists general applied “procedures”, but lacks any particular parameters. What MRI modes were used? What was an exact planning procedure for radiosurgical treatment? What criteria were used for evaluating the treatment efficacy and relapse development? How many patients underwent CT perfusion and/or PET-CT for differentiation between radiation necroses and tumor progression? A reference to the mentioned earlier works could answer these questions.

There is no data on spreading of the primary disease. To our opinion, different patient categories are described: in some patients, brain metastases are detected simultaneously with the
primary tumor, or perhaps the disease manifests in such a way; in others, brain metastases develop during treatment, at very different times from the primary verification of disease. These events may affect overall survival indicators in the same way as modern chemotherapy options can affect control of brain metastases, at least in most of affected patients (breast cancer, lung cancer with EGFR gene mutations, etc). Obviously, the retrospective analysis was complicated by the lack of data on these issues and on the course of disease (after radiosurgical treatment) and further treatment of disseminated cancers in the study group. However, if we ignore drawbacks in data collection for this complex and heterogeneous group of patients with brain metastases, we would hardly be able to improve significantly our approaches to treatment and early detection of these metastases.

We consider recent initiatives of radiologists from the Burdenko Neurosurgical Institute and the Gamma Knife Center to be particularly important. They proposed collaborative projects with experts from the largest cancer centers aimed at developing protocols for evaluation and treatment of patients with solid tumor brain metastases. We expect that these prospective studies will be conducted, which will improve our understanding of modern opportunities in the treatment of patients with disseminated cancers and brain metastases.

G.L. Kobyakov (Moscow, Russia)
Neuropathic pain comprises a significant part of all chronic pain syndromes. A total of 6 to 8% of the adult population suffers from it [1, 2]. According to the definition by the International Association for the Study of Pain (IASP), neuropathic pain is caused as a result of injury or disease of the somatosensory system. This type of pain is clinically characterized by a specific set of sensory disorders, which can be divided into two groups. On the one hand, these are irritation symptoms (spontaneous pain, allodynia, hyperalgesia, dysesthesia, paresthesia) and, on the other, they are symptoms of loss (hypoesthesia, hypalgesia) [3]. This type of pain is difficult to treat with drugs and greatly affects the patients’ ability to work and the quality of their life. These patients often suffer from disturbed sleep, depression and anxiety.

Many patients with neuropathic pain mistakenly take nonsteroidal anti-inflammatory drugs, which are ineffective in this type of pain. This is due to the fact that in neuropathic pain, the main pathogenetic mechanisms are not the processes of peripheral nociceptor activation but neuronal and receptor disorders, peripheral and central sensitization. It is more productive to use an integrated approach for the treatment of neuropathic pain[3]. Invasive methods of treatment (neurostimulation, morphine and baclofen pumps, rhizotomy, cordotomy, DREZ) have become actively used for the treatment of patients with drug-resistant pain syndromes in recent years. Neurostimulation is better for the treatment of neurogenic pain, whereas intrathecal administration of analgesics and anesthetics is more suitable for somatogenetic, usually oncogenic, pain [4]. Chronic epidural stimulation (ES) of the spinal cord, first proposed by C. Shealey et al. [5] in 1967, is an alternative treatment for patients with failed back surgery syndrome, complex regional pain syndromes, diabetic polyneuropathy, postherpetic intercostal neuralgia, and etc. Due to the continuous technical improvement, the method allows to select the parameters of neurostimulation that will be the most effective and comfortable for each patient.

ES of the spinal cord has been used for the treatment of drug-resistant chronic pain for over 40 years. The method is based on electrical stimulation of the posterior columns and dorsal roots through electrodes placed in the posterior epidural space. The electrodes are connected to a generator of electric pulses, which works on batteries. Stimulation of the posterior columns causes the feeling of "needles and pins" or tingling (paraesthesia) in a patient. For reduction of the intensity of pain syndrome, it is important that paresthesias completely cover painful areas on the body. Such covering in combination with pain minimization can be achieved by careful selection of stimulation parameters.

The objective of this research is to present our own experience of using chronic ES of the spinal cord in clinical practice and evaluate the efficacy of this method in the close follow-up.

**Material and methods**

A total of 136 patients (48 males and 88 females) aged 26 to 83 years (mean age 52.2 years) with various chronic neuropathic pain syndromes were operated on at the Federal Center of Neurosurgery in 2014. All patients had stable drug-resistant neurogenic pain syndrome. Exclusion criteria were: severe concomitant somatic

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pathology; incurable drug dependence; severe mental pathology; asynessia that made impossible the use of the system for chronic ES. All patients were informed at the selection stage about possibilities of the method, its limitations, possible complications, and expected outcomes.

On the first stage, transcutaneous implantation of test electrodes (Octrode, St. Jude Medical) was performed; test stimulation was carried out intraoperatively. If electrodes were placed properly, the area of paresthesias provided the maximum coverage of the pain site. Correction of the electrode position was conducted if necessary. Adjustment of stimulation parameters was performed on the next day. The mean test period was 7 days.

If a positive effect was obtained, the second step was performed: implantation of permanent electrodes (Octrode, St. Jude Medical) and generator (Eon-C, St. Jude Medical) in the supragluteal region.

Implantation of the permanent system was performed under local anesthesia with potentiation of narcotic analgesics. A linear incision in the region of LIII—LIV spinous processes was performed in the prone position. After visualizing aponeurosis, paramedian puncture of posterior epidural space was performed on the right and left sides with two Tuohy №14 needles. Two electrodes were extended under image intensifier control. The level of electrode installation was determined by localization of the pain syndrome. If the pain was localized in the lower limbs and back, the electrodes were mostly implanted at ThIX—ThXI level. In case of the pain localized in the upper limbs, implantation was conducted at CIV—CVI level. In case of perineal and pelvic pains, concomitant stimulation of the lower thoracic level of the spinal cord and sacral roots in the sacrum was used (by retrograde extension). Repetitive test stimulation was performed on the operating table. Upon reaching a satisfactory coverage of the pain area by paresthesias, Tuohy needles were removed, electrodes were fixed to the aponeurosis with plastic anchors. After this, the approach to the left supragluteal region was made, and the pocket in subcutaneous adipose tissue was formed. The generator was connected to electrodes pre-drawn through the subcutaneous tunnel. Then, damper rings were formed to prevent migration of the electrodes, and the wounds were sutured.

All patients underwent neurological examination with the assessment of pain syndrome according to the VAS and DN4 scales (neuropathic nature of the pain syndrome was confirmed in all patients) in the preoperative period, after implantation of test electrodes, after implantation of the permanent system, and then after 3, 6 and 12 months of using ES. In the follow-up period, pain intensity was monitored, correction of stimulation parameters was performed, and, if necessary, drug therapy was prescribed.

Results

A significant regression of pain syndrome (50% and more) was achieved in 75 (55.1%) patients in the test period. The group consisted of 28 males (37.3%) and 47 females (62.7%). The median age was 51.6 years (range: 26 to 83 years), the mean duration of pain syndrome was 80.9 months (range: 4 to 288 months). The distribution of patients according to nosology is presented in the Figure.

The vast majority of patients (53 persons, 70.7%) were diagnosed with failed back surgery syndrome (FBSS). The average number of surgeries prior to ES system implantation was 1.4 (0 to 5). Four (5.3%) patients experienced pain in the perineum, 11 (14.7%) patients had isolated limb pain, 60 (80.0%) patients had pain in the lower limbs in combination with axial pain (in breast or lumbar regions). The mean VAS score was 6.5 points (range: 5 to 10) prior to surgery, 3.2 at discharge, decreased to 3.1 after 3 and 6 months and amounted to 3.6 after 12 months. The mean DN4 score was equal to 5.3 before surgery and 2.1 at discharge.

Pronounced pain at the generator implantation site occurred in 2 patients (2.7%). No signs of wound/system infection have been observed. Conservative analgesic therapy failed to be effective, and the systems were removed. Migration of the electrodes occurred in 4 (5.3%) patients, which required repeated surgical intervention for reposition the electrodes.

Discussion

The efficacy of ES (the proportion of patients satisfied with treatment), according to various sources, ranges from 47 to 83% [6, 7]. The stimulation effect largely depends on pain location, disease duration, stimulation methods that have been applied, and adequacy of the patient’s expectations. The physiological mechanism of ES action is only partly explained by the gate control theory proposed by R. Melzack and P. Wall [8] in 1965, according to which the transmission of pain impulse is blocked by antidromic impulses passing through collateral fibers (tactile and vibration sensation) of the posterior columns. According to this interpretation, acute nociceptive pain should be also blocked by stimulation, but it does not happen. Post-stimulation analgesic effect of ES, which lasts 45 minutes on average, is difficult to explain. Apparently, the feeling of paresthesia in patient during stimulation is caused by orthodromic stimulation of myelinated fibers. According to C. Stiller et al. [9], hyperexcitability of association neuron, on which many axons of the posterior roots converge, is due to an increased release of glutamate and GABA system dysfunction. During stimulation, on the opposite, increased release of GABA occurs, which leads to inhibition of association neuron. Moreover, ES reduces the concentration of extracellular glutamate and aspartate in the dorsal horn [10, 11]. These effects are...
caused mainly by GABAB receptor activation [12]. It has been demonstrated on experimental models of neuropathic pain that the release of serotonin, glycine, adenosine and noradrenaline, which act on the descending pain pathways, occurs during stimulation. The cholinergic system is also involved in stimulation. The release of acetylcholine is explained by activation of M4 muscarinic receptors, while low doses of agonists of muscarinic receptors lead to the double effect of stimulation in rats, which is due to the involvement of descending inhibitory serotonin pathways, which also participate in pain modulation [13].

Positron emission study of the brain in patients with ES system installed on the occasion of neuropathic pain in the lower limbs revealed increased regional blood flow and metabolism in the contralateral thalamus and associative areas of pain sensitivity of the parietal lobe on both sides. Supraspinal centers of pain sensitivity transmission located in the brain stem are also activated during stimulation [14, 15]. ES causes some effect on the emotional component of pain through activation of the anterior regions of cingulate gyrus and prefrontal area [16].

Another effect of ES is peripheral vasodilation, which occurs due to reduction of the sympathetic system activity [17]. This effect is important for the treatment of patients with angina, complex regional pain syndrome of all types, chronic arterial insufficiency of the lower limbs accompanied by pain. Improved blood circulation in the limbs upon stimulation can be detected by Doppler ultrasound imaging, thermal imaging and other methods. In general, the mechanism of the analgesic action of ES includes the following processes: electrophysiological blockade of pain impulse transmission; production of endogenous antinociceptive substances (GABA, serotonin, glycine, norepinephrine, and etc.) and increase in the descending influences of the antinociceptive system; peripheral vasodilatation through the effect on the sympathetic nervous system; changes in emotional state through the impact on the limbic system.

Influence of pain localization on ES efficacy. According to the VAS scores, the patients who have quite moderate regression of pain syndrome upon chronic stimulation (VAS difference was approximately 2 points) were selected before and after surgery. This became the cause of lower satisfaction with the provided treatment. This group included patients with pain in the upper limbs, postherpetic intercostal neuralgia, perineal pain, and so-called “level” pain after spinal cord injury [18]. As for the patients with pain in the upper limbs, lower efficacy is partly accompanied by stimulation of instability, which, in turn, is due to the high mobility of the cervical spine, which leads to the displacement of the spinal cord and the roots relative to the electric field of the electrodes during flexion and extension. As a result, patients with implanted cylindrical electrodes return to the clinic with the head tilt when it is possible to cause paresthesia and pain relief. In these patients, analgesic effect is absent in the upright position, while quite painful stimulation can be observed in head tilt.

Significant disorders of sensation in the affected segment, which negatively affect ES efficacy, are usually found in patients who had suffered spinal cord injury and postherpetic intercostal neuralgia [19-21]. Patients with severe hypesthesia or anesthesia, as a rule, are excluded at the stage of selection or during the test period.

Significant regression of pain (VAS difference was about 5 points) was achieved in patients with diabetic neuropathy, isolated pain in the lower limbs and stump pain.

Pain in the lumbar region in patients with FBSS is worse amenable to treatment by stimulation, since paresthesias descend from lumbar region to the buttocks

**Distribution of patients according to nosology.**

FBSS — failed back surgery syndrome; CRPS — complex regional pain syndrome.

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level with time, which provides good analgesic effect in
the buttocks and legs, but back pain remains. It is known
that different anatomical areas can be covered by
paresthesias to different extents. J. Holsheimer and G.
Barolat [22] provided possible explanations for this
phenomenon in 1998. The first explanation is the
characteristics of the location of fibers from the
corresponding anatomical sites inside the posterior cords
and their availability for stimulation. The second one is
relative amount of fibers in the posterior cord representing
the zone, which can vary greatly. This is particularly
noticeable in the case when small and large amounts of
fibers from different anatomical regions are located in
close vicinity to each other in the posterior cord. For
example, paresthesias in the SI dermatome can be easily
achieved, which is explained by the fact that the SI root
consists of 12-15 fascicles. These fibers are then adjacent
to the posterior cords and form an extensive representation
of SI dermatome.

Using the ES method, it is quite difficult to achieve
an isolated stimulation of the perineum. We used
stimulation of the medullary cone (2 cases) and sacral
roots at the level of sacrum (2). The problem that limits
stimulation of roots in the spinal canal is their considerable
mobility. The roots are loosely located in the cerebrospinal
fluid and move with respiratory motions and change in
body position, so intensity and stimulation location vary
con siderably even when epidural electrode is installed
stably and are often accompanied by intense paresthesias
in the limbs. This is explained by the fact that the SII—
SIV roots are very small and often consist of only 2-3
fascicles, and their representation in the posterior cords
is considerably inferior to the area of SI dermatome.
Stimulation of the sacral roots in the posterior epidural
space of the sacrum is more stable and not accompanied
by paresthesias in the legs since the SI root is located
relatively far away.

Effect of pain duration on ES efficacy. S. Rizvi et al.
[23] analyzed the efficacy of ES in patients with different
duration of pain. Efficiency reaches 80% upon
implantation of ES system within 2 years after the
occurrence of pain. Patients suffering from long-term
neuropathic pain (for over 5 years) are less amenable to
treatment, and the efficacy of stimulation is lower in
them (not more than 47%). This is due to the peripheral
and central pain sensitization. The average duration of
pain was about 7 years in our sample. This is largely due
to the low availability of neuromodulation methods for
pain treatment in our country. An important factor is also
low awareness of doctors and patients on invasive
methods of treatment of neuropathic pain syndromes.

Stimulation methods. Optimization of the method to
achieve better clinical effect and improve the ease of use
for the patient is currently under an ongoing development.
For example, plate electrodes implanted at the cervical
level are less mobile and create a wider electric field
thereby providing more stable stimulation [24], which
can increase ES efficacy in patients with pain in the upper
limbs. High-frequency stimulation, in contrast to
conventional stimulation, is based on the use of higher
frequencies (2000 to 10000 Hz). There are no paresthesias
in this stimulation mode, which is better tolerated by
patients. In 2014, the data by the European randomized
multicenter clinical study were published, which included
test of the device involving 82 patients. Initially, patients
rated the pain in the back by an average of 8.4 points out
of 10. After 6 months of therapy, the mean pain score
decreased to 2.7 points. Most patients who participated
in the study stated more than 50% reduction in pain; 72
patients had a constant implanted pulse generator. After
24 months, VAS score in these patients remained
approximately at the same level [25]. Stimulation in this
mode requires more energy, which causes the need in
more frequent recharge or replacement of generator.

Stimulation of the spinal ganglion is especially
recommended in the treatment of monoradicular pain
syndromes or pain spread through only a few dermatomes,
which may be a solution for patients with postherpetic
intercostal neuralgia and pain in the upper limbs.

Adequate expectations of therapy. It is rarely possible
to achieve complete pain relief in case of neuropathic
pain, even when the treatment program is selected
properly. The method of chronic spinal stimulation has a
number of distinctive features in comparison with
traditional conservative or surgical treatment: 1) the
method is relatively minimally invasive; 2) mandatory
test stimulation; 3) permanent stimulation paresthesias;
4) side effects: the dependence of stimulation intensity
on the body position and possible migration of electrodes;
5) the need for generator replacement; 6) precautions
and limitations for the patient such as inability to
undergo MRI, take hot baths, and a necessity to wear a
permanent magnet for the emergency switching on/off of
the system, and etc. [26]. Therefore, it is extremely
important to hold a discussion with the patient and his
relatives, talk about the treatment method and its stages
as well as the subsequent restrictions in daily life before
starting therapy. This method considers active
involvement of the patient for achievement of the best
effect of the therapy [26].

Conclusion

The treatment of chronic neuropathic pain is a
complicated task, which does not have a sole correct and
easy solution. Chronic ES is an effective and safe method,
which allows significant reduction in pain intensity.
Careful selection of patients is the key to a successful
outcome. It is important to assess not only the nature of
pain, its intensity and location during selection but also
psychological state of the patient.

Authors declare no conflict of interest.
REFERENCES


Commentary

The authors have presented a very interesting article devoted to one of the most essential issues of modern medicine, the problem of chronic drug-resistant pain. Unfortunately, many neurologists, therapists and general practitioners conducting a long-term conservative treatment of patients with severe pain are not even aware of how this treatment can be ineffective and do not know the criteria and timing of the transition from conservative treatment to minimally invasive methods. In the current paper, the authors presented the most common of these methods, electrical stimulation (ES) of the spinal cord.

Attention is drawn to the sufficiently large number of patients included in the study. Despite the apparent prevalence of patients with failed back surgery syndrome, heterogeneity of the sample only endorses the value of this work and provides an opportunity to evaluate the results of treatment of various chronic pain syndromes. The surgery technique is presented in full (within such article format).

The need to conduct test ES remains open. The vast majority of authors consider it to be necessary. However, recently, there have been papers published that put the value of the test in question. In our experience, a test period is necessary. However, sufficiently rigorous selection should be carried out prior to test period based primarily on the psychological characteristics of patients. In order to evaluate the results, the authors used classical pain-VAS and DN4. The latter test, alongside with the classic Pain Detect and LANSS, is mostly used to confirm the neurogenic nature of pain, which can persist after surgery but with less severity. In connection with the stated above, the authors should use a questionnaire on the quality of life instead of DN4 in the future.

As a result of chronic stimulation of the spinal cord, good and stable analgesic effect was achieved in almost all patients. In addition, there were no serious complications. The incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. Neuromodulation. 2011;14:412-422.

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subcutaneous electrodes directly into pain area alongside with spinal cord ES). In the case of foot pain, the best results, according to the literature, are achieved by ES of dorsal ganglia. Unfortunately, this technique is not registered on the territory of the Russian Federation.

I should congratulate the authors with good results and wish them to continue the work in this direction, while expanding the spectrum of neurostimulation methods and indications for it.

_E.D. Isagulyan_ (Moscow, Russia)
Criteria of the Efficacy of Surgical Brain Revascularization in Patients with Chronic Cerebral Ischemia


Burdenko Neurosurgical Institute, Moscow, Russia

Purpose. The article analyzes results of surgical revascularization in patients with symptoms of chronic cerebral ischemia caused by occlusion of the carotid arteries.

Material and methods. We analyzed 404 surgeries for placement of extra-intracranial microvascular anastomoses (EICMAs) performed in 376 patients between 2000 and 2015. All patients underwent detailed neurological and neuropsychological examinations before surgery and throughout the follow-up period using the neurological deficit scale (NIHSS). Additionally, the medical history data, technical features of surgery, and results of instrumental tests were recorded. For a more detailed study of the cerebral circulation, a SCT perfusion examination was conducted in 58 patients before and after placement of EICMA.

Results. All patients were divided into 3 groups, depending on the surgical treatment outcomes: improvement (53%), without significant changes (43%), and worsening of clinical symptoms (4%). A statistical analysis revealed that the efficacy of EICMA surgery ranged from 22 to 79% and was reliably confirmed by hemodynamic and anamnestic factors as well as by technical details of surgery.

Conclusion. When determining the indications for surgical revascularization in patients with ischemic stroke consequences, the patient's age, occlusion duration, location and size of ischemic lesions should be considered. Also, the choice of the acceptor artery and blood flow through the created anastomosis are of great importance.

Keywords: cerebral revascularization, chronic cerebral ischemia, carotid arteries occlusion.

The problem of surgical brain revascularization in patients with chronic cerebral ischemia has been paid close attention since the first surgery on the establishment of extra-intracranial microvascular anastomosis (EICMA) performed by Yasargil in 1968. The reason for this is high epidemiological importance of symptomatic carotid artery occlusion in disability and mortality from acute ischemic stroke. Chronic cerebral ischemia is registered in 6 cases on average per 100,000 of population among patients with internal carotid artery (ICA) occlusion [1]. It is manifested by progressive cognitive impairment, limited social and labor adaptation as well as an increased risk of recurrent cerebral circulatory disorders (CCD): 8 to 21% per year [1, 2]. In such cases, surgical treatment remains to be the patients' last hope for help, which is proved by a lot of clinical observations.

Despite of long history of EICMA surgery application in patients with carotid artery occlusion, its role in cerebral ischemia treatment is being much debated by specialists nowadays. In contrast to carotid endarterectomy as a method of ischemic stroke prevention in patients with hemodynamically relevant stenosis (ICA), EICMA surgery in patients with atherosclerotic occlusions of ICA failed the trials by evidentiary medicine. The reason for this is a series of methodical shortcomings, the main one of which is the over-wide spectrum of indications for surgical cerebral revascularization (Bypass Study Group, 1985 [3]) and a high frequency of perioperative complications (COSS Trial, 2011 [2]). As a result, many patients are currently being denied necessary surgical interventions, while the performed EICMA surgeries are often of random nature [4]. The question of the impact of EICMA on the regression of neurological symptoms and improvement of rehabilitation prognosis in patients with the consequences of ischemic stroke also remains open.

Inconclusive results of international research on the use of EICMA surgery for improvement of rehabilitation prognosis gave rise to a detailed statistical analysis of the effectiveness of EICMA performed in patients with symptomatic carotid artery occlusion at the Institute of Neurosurgery n.a. N.N. Burdenko over the past 15 years and evaluation of the factors influencing this efficiency.

Material and methods

The results of 404 surgeries on the placement of EICMA in 376 patients with carotid artery occlusions performed at the Institute of Neurosurgery in the period of 2000-2015 have been analyzed. The age of patients ranged from 14 to 78 years (mean age 54.3 years). The main indications for surgery were occlusion of the internal carotid artery (ICA) (330 patients) and occlusion of the middle cerebral artery (MCA) (25 patients), moyamoya disease (18) with a clinical picture of chronic cerebral ischemia and symptoms of cerebrovascular insufficiency according to the preoperative ultrasound examinations (more than 50% decrease in linear blood flow in the MCA on the side of occlusion compared to the opposite side in combination with impaired cerebrovascular reserves). Initial indications were...
specified with the introduction of methods for studying cerebral perfusion into diagnostic algorithm.

In the majority of cases (302 patients), we detected the consequences of ischemic stroke corresponding to the side of ICA occlusion. Transient neurological symptoms in the form of frequent TIA or minor ischemic stroke were detected in 56 patients. A total of 15 patients showed signs of vascular encephalopathy only.

The diagnostic algorithm included a detailed neurological, neuropsychological and neuro-ophthalmological survey. The US National Institute of Health Stroke Scale (NIHSS) has been used for objectification and quantification of neurological and cognitive deficits. For the study of morphological changes in the brain, all patients underwent CT or MRI examinations. Localization and the size of ischemia foci were assessed according to the well-known ASPECTS scale in 10 regions of the MCA (10 points in the absence of ischemia foci, 0 points in case of lesion of all MCA circulation) [5]. In order to verify the diagnosis and study collateral blood flow in the occluded artery circulation, comprehensive ultrasound data were supplemented with angiography performed predominantly non-invasively (CT/MR angiography).

The surgery on the establishment of EICMA was performed according to standard methods, in most cases it was conducted on MCA cortical arteries. Anastomoses with the proximal regions of MCA (M2—M3) were placed in 13 patients. In addition, 13 patients underwent double anastomoses of both branches of the superficial temporal artery (STA). Technical details of the conducted surgical interventions were taken into account upon statistical analysis of the efficiency of performed surgeries.

The efficacy of surgical brain revascularization was assessed in the immediate postoperative period and during follow-up. The duration of follow-up ranged from 1 to 138 months (mean 42.25±31.90 months). The follow-up was not tracked for 12 (3.2%) patients, including patients who died after surgery. The distribution of follow-up duration is shown in Fig. 1a. In total, a year’s follow-up data were collected for all patients, and the follow-up for the period of up to 3 years was tracked for 317 (84%) patients.

We controlled anastomosis function, measured the change in volumetric flow rate in it according to the standard technique during control examination. The dynamics of neurological deficit were evaluated by repeated neurological and neuropsychological examination in accordance with the NIHSS scale.

Processing of the study results was carried out using IBM SPSS 20.0 software for statistical processing.

**Results**

Positive dynamics of clinical symptoms were detected in 260 (69%) patients during the follow-up period. Transient ischemic attacks, which were observed in 141 patients before surgery, regressed completely in 134 (95%) cases after the placement of EICMA. Recurrent cerebral circulation disturbances of ischemic type were detected in total in 43 (11.4%) patients during follow-up including 7 (2.3%) of them in the circulation of established EICMA, in the form of TIA (4 cases) and ischemic stroke (3). All recurrent CCD were characterized by easier clinical course with a significant reduction of symptoms to the level of early postoperative period. There were no registered CCD fatalities in the circulation of revascularization.

After the establishment of EICMA, an increase in neurological deficit was noted in 12 cases, which was associated with the development of perioperative complications. Postoperative mortality equaled 0.7%: 3 patients, who were operated on in the acute period of ischemic stroke on the background of its malignant course, died. Taking into account the lack of opportunity to identify the role of EICMA in these observations, they were excluded from the further analysis.

For objectification of changes in clinical status after placement of EICMA, patients underwent neurological examination with the quantification of the value of neurological deficit according to the NIHSS scale during follow-up. A significant regression of neurological symptom was noted in the analyzed group, which amounted to an average of 2.03±1.23 points (p<0.041; CI [1.25–2.57]), i.e., 25% of the initial average value of neurological deficit. The degree of neurological deficit restoration varied (see Fig. 1b). All analyzed patients were divided into three main groups depending on the results of control neurological examination.

The 1st group consisted of 199 (53%) patients with objective symptoms of neurological deficit reduction of more than 2 points according to the NIHSS scale, and complete regression of transient neurological symptoms.

The 2nd group included 162 (43%) patients without objective symptoms of reduced neurological symptoms or signs of subjective improvement within 2 points according to the NIHSS scale.

The 3rd group consisted of 12 (4%) patients with worsened neurological symptoms.

In order to determine the groups of patients with carotid artery occlusions, in whom the surgery on the establishment of EICMA had the greatest clinical efficacy, a statistical analysis of the main factors influencing surgery outcome was conducted. As a result, it has been found that outcomes of EICMA surgery were reliably determined by hemodynamic, anamnestic factors, as well as the technical features of the surgical intervention.

The results of statistical analysis are presented in Table 1.

It is characteristic that one of the most significant factors that affected the outcome of surgery was the clinical course of the disease (χ²=21.41; p=0.027). For instance, the greatest clinical effect of surgery was
observed in patients with transient neurological symptoms and small strokes (TIA, MS): 78.5% of the cases. In this case, the main purpose of surgical revascularization of the brain was to prevent the development of a broad hemispheric ischemic stroke due to severe cerebrovascular insufficiency diagnosed in patients. The diagnostic algorithm that was originally used in the study was also aimed at identification of this group of patients and reflected the common belief of the preventive role of EICMA in patients with symptomatic occlusions of ICA. That is why the obtained results were expectedly the same as results of the earlier studies [6, 7], which showed high efficiency of cerebral revascularization in patients with transient neurological symptoms.

Patients with the signs of dyscirculatory encephalopathy or vertebrobasilar insufficiency often lacked positive dynamics of the clinical status (60% of cases). In addition, a higher incidence of worsened clinical course in the postoperative period (13%) was noted for this group of patients, which allows assuming EICMA surgery to be inappropriate for patients with chronic occlusions of the ICA that are manifested only by cerebral or non-specific symptoms.

The distribution of the outcomes of EICMA surgery in patients with consequences of ischemic stroke were not statistically different from the average for the entire sample and depended mainly on other factors. An objective improvement of neurological symptoms was observed in 51% of cases, which explains the ambiguous attitude of the specialists to medical (restorative) role of EICMA in patients with the consequences of ischemic stroke [6-9]. Analysis of the causes of inconclusive results of EICMA indicates, apparently, the need to clarify the indications for the placement of EICMA in this group of patients, which take into account both the possibility of lost function restoration (neuroplasticity) and the degree of persistent perfusion deficit. The factors influencing the patient's ability for neurological deficit recovery will be studied in the current paper. The study of perfusion factors of the efficiency of EICMA surgery will be discussed in a separate publication.

Another important factor significantly influencing the outcome of EICMA surgery was the patient's age ($p<0.05$, $|Z|=1.989$). The youngest age was observed in patients with pronounced clinical improvement (43.1±5.1 years), whereas patients with an increasing neurological deficit during the follow-up had the highest age (62.6±8.2 years). These data can be explained by the great abilities for recovery at a younger age and the reduction of compensatory possibilities of cerebral blood flow and cerebral metabolism with organism aging.

One of the most important statistically significant factors determining the outcome of surgical revascularization of the brain was the duration of ICA occlusion ($\chi^2=177.2; \ p<0.001$). As it can be seen from table 1, a very low efficiency of EICMA was noted in patients with more than a year-long occlusion (only in 7% of cases) regardless of the volumetric blood flow in anastomosis. In patients with high hemodynamic significance of EICMA in postoperative period, the signs of hyperfusion syndrome in the form of increasing paroxysmal and extrapyramidal symptoms, emotional and personality disorders (aggression, euphoria, tearfulness, emotional lability) were often revealed instead of reduced neurological deficit. The results obtained in this group of patients correlate with the transition from late recovery period to the period of persistent neurological changes in accordance with the classification of the terms of acute ischemic stroke by E.I. Gusev et al. [13].

The greatest clinical effect of EICMA surgery developed in the period of up to 1 year after surgery (up to 70% of cases). Moreover, a reliably high incidence of ischemic complications of the surgical treatment reaching up to 10% was registered in patients with acute and subacute CCD (up to 3 months). High risk of complications in this group of patients, apparently, was associated with unstable hemodynamic balance developed after CCD [14]. Similar results were also noted during well-known multicenter international

**Fig. 1.** Histogram of the distribution of follow-up duration (a) and dynamics of neurological deficit according to the NIHSS scale (b) in patients after placement of EICMA (376 patients).
study COSS: the frequency of complications in patients with up to 3-month occlusion was 15% [15].

An important factor influencing the effectiveness of surgical revascularization in patients with chronic cerebral ischemia was the state of brain tissue determined according to tomography results. As it can be seen from table 2, the patients in the improvement group showed prevalence of the intact brain tissue in the MCA circulation (8.87±0.43 ASPECTS points) compared to the group of patients without clinical dynamics (7.4±0.33 ASPECTS points). This difference was statistically significant (p=0.043; |Z|=1.99700) and reflected the well-known negative impact on the size of ischemic focus on rehabilitation prognosis [8, 16]. Another negative factor was the presence of ischemic focus in the region of the basal ganglia: there were no dynamics of neurological deficit in 86% of these patients after placement of EICMA. This observation confirms previously obtained findings [6, 7, 17]. Nevertheless, clear positive dynamics of clinical symptoms after the placement of EICMA was noted in 14% of patients with lesions of the subcortical structures. In particular, the improvement of speech production was noted in the left-sided lesions in patients with aphasic disorders. The efficacy of EICMA surgery in regard to motion activity in patients with lesions of the subcortical structures was observed in the persistent perfusion deficit in the areas of unmodified white matter and functionally important areas of the cerebral cortex in the presence of the signs of intactness of corticospinal tracts. In such cases, we believe that it is appropriate to conduct MR tractography for clarification of rehabilitation prognosis and indications for surgical revascularization of the brain.

A strong statistically significant symptom influencing the efficiency of EICMA surgery is the localization of ischemic lesion of the brain in the areas of adjacent circulation (p<0.001, Student’s t-criterion): signs of regression of neurological symptoms were noted in 73% of such cases. Ischemia or the presence of glial changes according to T2-FLAIR MRI in these areas indicated the involvement of hemodynamic mechanisms in the pathogenesis of CCD [18], so the surgical correction of cerebral hypoperfusion in such cases in most cases led to improved neurological status (p<0.001; Student’s t-criterion).

Patients with a variety of outcomes of surgical treatment were comparable in terms of their pre-adaptation (by the Rankin scale) and the value of initial neurological deficit (by NIHSS scale). The study also revealed no significant impact of the patient’s gender on the surgical outcomes.

The second group of factors reflected the technical features of surgical revascularization of the brain. Their analysis is presented in table 2.

Statistical analysis revealed no significant influence of a donor artery selection (frontal/parietal branches of the STA) on the efficiency of EICMA. Leading factors were, primarily, its size and the amount of blood flow through it in accordance with which the donor artery was chosen.

Choice of the recipient artery had a greater impact on the outcome of surgical revascularization of the brain (χ²=61.22; p=0.003). The efficacy of revascularization of

<table>
<thead>
<tr>
<th>Table 1. Role of various factors in the outcomes of EICMA surgery in patients with symptomatic occlusions of carotid arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Patient’s gender:</strong></td>
</tr>
<tr>
<td>males</td>
</tr>
<tr>
<td>females</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
</tr>
<tr>
<td><strong>Value according to the NIHSS scale prior to surgery, points</strong></td>
</tr>
<tr>
<td><strong>Value according to the Rankin scale, points</strong></td>
</tr>
<tr>
<td><strong>Clinical course:</strong></td>
</tr>
<tr>
<td>DEP/VBI</td>
</tr>
<tr>
<td>TIA/MS</td>
</tr>
<tr>
<td>stroke</td>
</tr>
<tr>
<td><strong>Occlusion duration:</strong></td>
</tr>
<tr>
<td>up to 3 months</td>
</tr>
<tr>
<td>up to 1 year</td>
</tr>
<tr>
<td>more than 1 year</td>
</tr>
<tr>
<td><strong>The size of ischemia focus (ASPECTS)</strong></td>
</tr>
<tr>
<td><strong>Ischemia in ZAC</strong>*</td>
</tr>
<tr>
<td><strong>Ischemia in BG</strong>**</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

*Footnote.* **ZAC** — zone of adjacent circulation; **BG** — basal ganglia. 1,2Mann-Whitney criterion for paired comparison of the 3rd group with groups 1 and 2; 3Precise Fisher criterion.
the temporal and parietal regions was significantly higher (frontal central and precentral branches of the MCA, upper parietal branch, angular branch), which was due to their greater functional significance. Revascularization of the branches of the M4 level of the MCA supplying the temporal lobe (anterior, middle and posterior temporal branches) had statistically significantly lower clinical efficacy in 20% of cases and in the absence of the dynamics of neurological status in 78% of cases. A possible explanation for the obtained result could be in the preferred revascularization of the functionally meaningless temporal region, especially on the right side. When choosing the temporal cortical recipient artery, revascularization of the frontal areas is possible only in case of significant amounts of volumetric blood flow through the donor artery that can cause significant hemodynamic reconstruction in the MCA circulation up to the reversal of blood flow in the MCA branches to M1—M2 segments on the side of occlusion [19].

The selection of the temporal cortical branch of the MCA for EICMA is unadvisory in patients with moyamoya disease or extended occlusion of M1 segment of the MCA as well as in cases when donor arteries are of small diameter (1 mm or less); cerebral revascularization is limited only by temporal lobe, which reduces the effectiveness of surgical treatment.

Analysis of the efficacy of proximal revascularization in our group demonstrated no statistically significant advantages in comparison with other acceptor arteries: improvement of the clinical symptoms was noted in 62% of cases despite higher volumetric flow through anastomosis in this group of patients (54.6±4.3 ml/min). Also, a higher incidence of perioperative ischemic complications in the group of proximal EICMA should be noted, which reached 15% and was apparently associated with the temporal cross-clamping of the major branch of MCA on the background of reduced perfusion pressure.

An alternative to anastomoses with the proximal regions of MCA in patients who require restoration of blood flow in a broader area of perfusion deficit was the use of double EICMA (13 surgeries) between cortical arteries and both branches of the STA (Fig. 2).

This type of revascularization allows achieving high volumetric blood flow through anastomoses (average 58.7±6.2 ml/min) at a lower rate of complications. No surgical complications were observed in all of the analyzed observations. The only case (7.7%) was minor stroke associated with thrombosis of both branches of anastomosis and developed in the early postoperative period (day 4). We managed to achieve clear positive dynamics of clinical symptoms in all of the other cases (92.3%). Thus, the use of two anastomoses can be considered the choice of surgery for patients with severe perfusion deficit. Intraoperative navigation systems (selective revascularization) can be used for more optimal choice of recipient arteries in the circulation of greater cerebral ischemia.

The skills for placement of vascular anastomoses influenced the terms of cortical artery cross-clamping necessary for anastomosis formation. Average time of recipient artery cross-clamping in patients of the 1st and 2nd groups was 33.4±6.7 min (19 to 80 min), while there were no statistically significant differences between the groups. In patients with worsened clinical symptoms (the 3rd group), duration of the main phase of reconstruction was higher: 41.2±4.7 min. This difference was statistically significant (p=0.043, Mann-Whitney test) and pointed to the potential risks of ischemia development in patients with impaired cerebral hemodynamics in response to temporary exclusion of even M4 segment artery from the blood flow [15, 20]. Similar results were obtained during international cooperative study COSS [15]: a significantly longer duration of cortical branch cross-clamping, usually more than 40 minute-long (median 54 minutes), was noted in patients with complications.

One of the main factors influencing the outcome of surgical revascularization of the brain was volumetric flow rate through EICMA. As can be seen from Table 2, a significantly high hemodynamic efficiency of the placed

### Table 2. Influence of surgical factors on the results of revascularization of the brain. Analysis of 404 surgeries

<table>
<thead>
<tr>
<th>Factor</th>
<th>n</th>
<th>Improvement (group 1)</th>
<th>Without dynamics (group 2)</th>
<th>Worsening (group 3)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor artery</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parietal</td>
<td>327</td>
<td>165 (50%)</td>
<td>168 (48%)</td>
<td>7 (2%)</td>
<td>insufficient</td>
</tr>
<tr>
<td>frontal</td>
<td>64</td>
<td>41 (64%)</td>
<td>18 (28%)</td>
<td>5 (8%)</td>
<td>p=0.057</td>
</tr>
<tr>
<td><strong>Acceptor artery:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M4 angular</td>
<td>188</td>
<td>112 (60%)</td>
<td>71 (37%)</td>
<td>5 (3%)</td>
<td>χ²=61.22</td>
</tr>
<tr>
<td>M4 frontal</td>
<td>89</td>
<td>56 (63%)</td>
<td>32 (36%)</td>
<td>1 (1%)</td>
<td>p=0.0029</td>
</tr>
<tr>
<td>M4 temporal</td>
<td>101</td>
<td>20 (20%)</td>
<td>78 (78%)</td>
<td>3 (3%)</td>
<td>χ²=0.05</td>
</tr>
<tr>
<td>M2—M3</td>
<td>13</td>
<td>8 (62%)</td>
<td>3 (23%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>13</td>
<td>10 (77%)</td>
<td>2 (15%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Cross-clamping time</td>
<td>31.2±3.2</td>
<td></td>
<td>34.8±1.8</td>
<td>41.2±4.7</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Blood flow through/ EICMA</td>
<td>46.7±2.6</td>
<td></td>
<td>29.7±4.7</td>
<td>38.1±13.2</td>
<td>p=0.05</td>
</tr>
</tbody>
</table>

1. Analysis of only single EICMA. 2. Mann-Whitney criterion for paired comparison of the 3rd group with groups 1 and 2; 3. Student’s t-test for paired comparing of the 1st and 2nd groups.
anastomoses was noted in patients of the 1st group, which amounted to an average of 46.7±6.2 ml/min. In patients with pronounced regression of neurological deficit (more than 3 points according to the NIHSS scale), the volumetric blood flow through EICMA reached 51.8±3.4 ml/min. The obtained values were statistically significantly higher than the amount of volumetric blood flow in the group with the absence of clinical effect: 29.7±4.7 (Student’s t-criterion; p=0.0445). This indicates the role of hemodynamic significance of EICMA not only in the prevention of recurrent CCD, but also in improvement of rehabilitation prognosis in patients who suffered ischemic stroke. In particular, the improvement of clinical status was not observed in all patients with postoperative EICMA thrombosis (18 (4.2%) cases in total among all surgeries).

Discussion

The proper determination of indications for the placement of EICMA is the key to clinical efficacy of this surgery in patients with symptomatic occlusions of carotid arteries. In addition to known hemodynamic criteria for the selection of patients for anastomosis placement, there are additional factors that have a significant impact on the outcome of surgical intervention. As seen from the presented statistical analysis, it is advisable to use a differentiated approach for determination of indications for surgical revascularization of the brain depending on the clinical course of cerebral ischemia.

For instance, patients with transient or soft neurological symptoms (minor stroke) in the early period after ICA occlusion require, first of all, stabilization of the clinical symptoms and prevention of recurrent cerebrovascular disturbances. The main criterion for the potential effectiveness of EICMA surgery in this group is the signs of severe cerebrovascular insufficiency detected according to comprehensive ultrasound, SCT/MR perfusion imaging and PET. The use of such criteria enabled effective EICMA surgery in patients with unstable clinical symptoms in 79% of cases. At the same time, the signs of decompensation of cerebral circulation explain increased risks of perioperative complications of surgical treatment, which were identified in 7% cases on average and in 10% cases upon placement of EICMA in the period of up to 3 months from the development of occlusion. The obtained results are confirmed by the data of recent multicenter COSS study [15]: the incidence of ischemic complications in patients with grade II CVI reached 15% in the period of up to 3 months. In such cases, it is necessary to plan the surgery and anesthetic management in order to maximize brain protection at the main stage of surgery. It is advisable to perform the differential diagnosis of the course of ischemic stroke in the case of unstable clinical course in the form of TIA or progressive neurological deficits: in such cases, it is recommended to adjust drug therapy at the first stage due to extremely high risks of perioperative complications and mortality.

The use of similar criteria for patients with the consequences of ischemic stroke (more than 2 points according to the Rankin scale) is, apparently, insufficient, since it is clinically effective only in 51% of cases. A possible explanation of this fact is the difference of the pathogenetic mechanism of chronic cerebral ischemia in patients after ischemic stroke, which is, first of all, characterized by incomplete recovery of cerebral perfusion. This, in turn, may cause the persistent neurological deficit that is difficult to rehabilitate [21]. Despite the fact that such conditions are rarely accompanied by recurrent CCD, they are regarded as pathological since they prevent restoration of the lost function and are among the causes of cerebral degeneration [22, 23]. There are cases of neurological deficit regression and improvement of rehabilitation prognosis after restoration of cerebral perfusion due to leveling of the effects of afferent diaschisis documented in the literature [23, 24].

In such cases, the main goal of EICMA surgery is the creation of favorable conditions for restoration of lost functions. When determining the indications for surgical revascularization of the brain, it is important, in addition to determination of the signs of persistent cerebral circulation insufficiency, to properly assess individual capabilities of neuroplasticity associated with the patient’s age, duration of occlusion as well as the size and foci of brain damage.

Thus, the optimal terms of surgical treatment are within 3 months to 1 year. In terms of more than 1 year after the development of occlusion, the decreased regional blood flow is usually balanced by the atrophy with glial transformation of the brain tissue, which is accompanied by a decrease in metabolic needs of the brain. This explains low risks of recurrent CCD in occlusion circulation in combination with poor rehabilitation prognosis [13]. In such cases, an additional source of blood supply to the brain, apparently, becomes excessive, which, in turn, was confirmed by low EICMA efficiency (22%). The presence of extensive ischemia foci with lesions of subcortical structures and the patient’s age older than 70 years also negatively influenced EICMA efficiency.

It should be noted that the efficacy of EICMA significantly depended on the volumetric blood flow through EICMA. This fact confirms the contribution of EICMA in the process of lost function recovery in patients during follow-up. In this regard, much attention should be paid to the quality of the placed anastomosis, its throughput capacity as well as the correct choice of recipient artery. More frequent use of double EICMA with both STA branches is reasonable in case of cerebral revascularization.
The introduction of modern methods of studying cerebral perfusion parameters (CT and MRI) into clinical practice allowed more detailed research of cerebral blood flow in candidates for surgical revascularization of the brain. In particular, due to the greater objectification of the signs of cerebrovascular insufficiency using SCT perfusion examination, it became possible not only to assess overall hemispheric but also local changes in the tissue blood flow in the cortex and white matter of the brain. A detailed analysis of perfusion criteria of the efficiency of EICMA surgery will be presented in the next publication.

The obtained results are consistent with the previous studies on surgical revascularization of the brain in patients with chronic cerebral ischemia. At the same time, a comprehensive analysis of various factors allowed selection of a group of patients with high efficiency of EICMA. The urgency of the problem of surgical
treatment of symptomatic occlusions of carotid artery circulation still remains to date, which provides a high demand for new large cooperative multicenter studies. The available results and the presented approach for the determination of indications for EICMA surgery can be taken into account upon their planning.

Conclusion

1. Taking into account the differences in the clinical course and cerebral perfusion in patients with the consequences of ischemic stroke and transient or soft neurological symptoms (minor stroke), a differentiated approach should be used for the determination of indications for EICMA surgery depending on its purpose: prevention of ischemic stroke or improvement of rehabilitation prognosis.

2. EICMA surgery is effective in patients with TIA or minor (non-incapacitating) stroke and the signs of severe cerebrovascular insufficiency for prevention of recurrent CCD while reducing the incidence of perioperative complications.

3. The clinical efficacy of EICMA depends on its hemodynamic significance (volumetric blood flow through anastomosis) as well as individual features of neuroplasticity, which are determined by the patient’s age, duration of occlusion as well as the size and foci of brain damage.

4. The placement of EICMA is unadvisable in the cases of long-term ICA occlusion (more than 1-year duration), in the case when the patient’s age is over 70, in vast focal lesion of MCA circulation as well as the signs of compensation of cerebral circulation.

Authors declare no conflict of interest.

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The urgency of the issue discussed in the paper does not cause objections in connection with a high incidence of incapacitation and mortality from ischemic stroke, one of the leading causes of which are occlusions of the internal carotid arteries. EICMA surgery has been used in such cases for a long time. However, there is still an ongoing discussion in the domestic and foreign literature on its efficiency and advisability, especially in patients with the consequences of ischemic stroke. The results of the last major multicenter COSS study make the overall picture of indications for brain revascularization even more confusing. The criteria it proposes for the selection of patients for surgical treatment are based on the brain PET with oxygen isotope, an extremely expensive, difficult, and rare procedure, which is currently unavailable in the Russian Federation. As a result, there is a contradictory situation, when many patients are denied EICMA surgery, and at the same time the surgery is performed on unreasonable grounds in some cases. This explains the high relevance of the critical reconsideration of known indications for EICMA surgery in patients with chronic cerebral ischemia.

In the current article, the authors performed a complicated statistical analysis of the efficacy of EICMA surgery for the treatment of cerebral ischemia using modern apparatus of evidentiary medicine. The results of the conducted statistical analysis are pathophysiologically reasonable and do not cause significant objections. The individual approach offered by the authors for formulation of indications for EICMA surgery based on the differences between patients with transient neurological symptoms and the consequences of the ischemic stroke is also peculiar.

Undoubtedly, the problem of the advisability of EICMA surgery should be addressed within the framework of multicenter clinical studies involving neurosurgeons, neurologists and rehabilitation specialists. The results obtained in the article prove advisability of such studies in the future and can be actively used for their conduction.

There have not been any works with such study design in the recent years. The article is of great interest for neurologists and neurosurgeons dealing with the problem of cerebral ischemia treatment.

V.A. Lazarev (Moscow, Russia)
A Case of Successful Exclusion of a Middle Cerebral Artery Aneurysm Using Combined Revascularization Surgery

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Objective The study objective is to present a clinical case of successful surgical treatment of a complex middle cerebral artery (MCA) aneurysm using various bypass types.

Material and methods. A 59-year-old female patient presented with nontraumatic intracranial hemorrhage caused by rupture of a complex right MCA aneurysm. The anatomical features of the MCA aneurysm were identified using computed tomography (CT) of the brain in angiographic and 3D modes. The surgical intervention included aneurysmectomy and an end-to-end reanastomosis between the M1 and M2 segments of the MCA, followed by an extra-intracranial microvascular anastomosis (EICMA) between the frontal branch of the right superficial temporal artery (STA) and the cortical branch of the right MCA located on the frontal lobe surface.

Results. The intraoperative blood flow via the intra-intracranial bypass (IC-IC bypass) was 30 mL/min, and the linear blood flow velocity (LBFV) was 50 cm/s; the blood flow and LBFV via the STA-MCA bypass were 7—8 mL/min and 15 cm/s, respectively. CT angiography of the brain performed on the 1st postoperative day revealed the patency of the IC-IC and STA-MCA bypasses. The patient was discharged in satisfactory condition (Glasgow Outcome Scale — V) 1 month after surgery.

Conclusion. Revascularization surgery is a sought-after surgical technique for management of complex intracranial aneurysms, which enables efficient exclusion of the aneurysm from blood flow and prevention of ischemic brain injuries in the parent artery territory.

Keywords: complex intracranial aneurysm, revascularization, STA-MCA bypass, intra-intracranial (IC-IC) bypass.

The concept of “complex intracranial aneurysms” was introduced in neurosurgical practice to refer to aneurysms that usually cannot be efficiently excluded from blood flow by using only reconstructive procedures, such as microsurgical clipping or endovascular surgery. The very concept “complex aneurysm” is somewhat vague because each author dealing with the problem uses his own criteria of “complexity”. The basic conventional parameters of complex aneurysms were summarized in an article by L. Sekhar et al. [1] and elaborated in a publication by R. Hanel and R. Spetzler [2]: a wide neck (the dome/neck ratio is less than 1.5); the absence of the neck ( fusiform, saccular-fusiform, and blister aneurysms); pronounced atherosclerotic changes in the neck region; thrombosis of the aneurysm cavity; significant arteries originating from the aneurysm dome or neck; dissecting aneurysms; giant aneurysms (over 25 mm in one of the diameters); a difficult-to-reach localization of the aneurysm (vertebrobasilar basin, cavernous and ophthalmic segments of the internal carotid artery); insufficient collateral circulation in the area of efferent branches; “surgical history” of the aneurysm.

Each complex aneurysm requires an individualized choice of a surgical technique and careful preoperative planning; however, the final decision about a procedure for exclusion of the aneurysm from the circulation is usually made intraoperatively.

Here, we present a clinical case of successful treatment of a patient with a complex ruptured aneurysm of the right middle cerebral artery (MCA) who was treated using two types of revascularization interventions: an intra-intracranial end-to-end anastomosis (a reanastomosis in a classification by M. Lawton and N. Sanai [3]) and an extra-intracranial microvascular anastomosis (EICMA) between the frontal branch of the right superficial temporal artery (STA) and the cortical branch of the right MCA.

Clinical case. A 59-year-old female patient K. was transferred to the Critical Care Department of the Sklifosovsky Research Institute of Emergency Care from another hospital. According to the medical history, the patient suffered from headache for the past 2 years and was treated conservatively, without significant improvement. In December 2014, the patient had an episode of severe headache with loss of consciousness; she received outpatient treatment from a local neurologist. The present deterioration in the form of sharp shock-like headache and loss of consciousness occurred on February 02, 2015. Computed tomography (CT) of the brain revealed subarachnoid-parenchymal-ventricular hemorrhage; the patient was transferred to the Sklifosovsky Research Institute of Emergency Care. The patient’s condition at admission was serious; mechanical ventilation was performed. In the neurological status, depression of consciousness to sopor (12 points on the Glasgow Coma Scale (GCS)) and meningeal syndrome in the form of severe neck stiffness were observed. CT and CT angiography of the brain confirmed subarachnoid-parenchymal-ventricular hemorrhage and revealed a large aneurysm of the M1 and M2 segments of the right MCA (Fig. 1).
The aneurysm was assessed as complex according to the following criteria: the localization at the right MCA bifurcation, with hypoplasia of one of the M2 segments and branching of the segment from the aneurysm body; a wide aneurysm neck and an acute angle between the afferent segment (M1) and the main efferent segment (M2), which prevented clipping or stenting with formation of the parent artery lumen. We decided to exclude the aneurysm from the circulation and then to perform revascularization surgery during the “cold” period of hemorrhage, given the severity of patient’s condition (Hunt-Hess score IV) and a large amount of planned reconstructive surgery.

The patient was re-admitted to the Department of Emergency Neurosurgery of the Sklifosovsky Research Institute of Emergency Care in July 2015. The patient’s condition at re-admission was satisfactory. The patient’s neurological status was as follows: clear consciousness, no focal and meningeal symptoms. The patient underwent an examination with allowance for planned reconstructive surgery, transcranial dopplerography (TCD), ultrasound of the radial arteries, triplex scanning of the brachiocephalic arteries, electroencephalography, and the Allen’s test in both arms.

The patient underwent eloquent surgery, the first stage of which included extensive dissection of the right lateral fissure with identification of the aneurysm. The complex nature of the aneurysm was confirmed: the M1 and main M2 segments of the right MCA were located at an acute angle to each other at a distance of 2—3 mm; the second M2 segment coming out of the aneurysm body was hypoplastic (Fig. 2a).

The linear blood flow velocity (LBFV) recorded by means of a contact micro-Doppler probe was 55 cm/s in the M1 segment, 45 cm/s in the main M2 segment, and 10 cm/s in the hypoplastic M2 segment. By using preventive temporary clipping of the main M1 and M2 segments, we dissected the aneurysm body and tried to isolate the second M2 segment. We found that the M2 segment was tightly adhered to the aneurysm wall. Given the relationships of afferent and efferent vessels and impossibility of clipping the aneurysm neck, we excised the aneurysm body and transected the hypoplastic M2 segment. After aneurysm excision, an end-to-end reanastomosis between the M1 and M2 segments of the right MCA was performed. This surgery stage was performed using anesthesia care with mild hypothermia up to 34.5 °C and barbiturates for achieving the burst suppression effect that was confirmed by BIS monitoring. During the second stage, an EICMA between the frontal branch of the right STA and the cortical branch of the right MCA located on the frontal lobe surface was performed. Blood flow and LBFV were 30 mL/min and 50 cm/s, respectively, via the IC-IC bypass and 7—8 mL/min and 15 cm/s, respectively, via EICMA (Fig. 2b—h).

After the patient’s recovery from sedation 12 h after the surgery end, the level of wakefulness was assessed as moderate obtundation (14 points on the GCS); monoparesis of up to 4 points in the left arm was observed. One day after surgery, consciousness was clear, and the monoparesis regressed.

CT, CT angiography, and CT perfusion of the brain on the 1st postoperative day (Fig. 3a—e) confirmed functioning of the IC-IC and STA-MCA bypasses and revealed ischemic changes in the right frontal and temporal lobes, 21 cm³ in size, without transverse and axial dislocations.

An ultrasound examination on the 1st postoperative day confirmed functioning of the EICMA on the right, with LBFV of up to 25 cm/s and blood flow of up to 35 mL/min. According to TCD on day one after surgery, LBFV was 96 cm/s in the right MCA and 96 cm/s in the left MCA.

The patient’s condition at discharge one month after surgery was satisfactory; consciousness was clear; focal and meningeal symptoms were absent (Fig. 3e, f). The GOS score was V. According to TCD at discharge, LBFV in the right MCA was 83 cm/s. According to control ultrasound at discharge, LBFV via the EICMA was 30 cm/s, and blood flow was 40 mL/min.

Discussion

As early as in 1979, K. Miller and R. Spetzler et al. [4] performed an anastomosis between the middle meningeal artery and the cortical branch of the MCA, which may be formally attributed to IC-IC bypasses. The first reports on IC-IC bypasses appeared in the 1980s [5, 6], but this area began to develop most intensively in the early 1990s [7—9]. In recent years, interest in these interventions has been steadily increasing despite the development of endovascular surgery [2, 10—15]. In the domestic literature, experience with these interventions is presented by two publications [16, 17].

Intra-intracranial bypasses are more suitable to the normal anatomy and are more physiological compared to extra-intracranial high-flow bypasses and do not require additional cuts in the neck and, in most cases, harvesting of autografts (radial artery or great saphenous vein). They enable restoration of cerebral blood flow through pathways very close to the normal ones [3]. However, the technique for placement of these anastomoses is more complex compared to that for EC-IC anastomoses, given the need to manipulate within a narrow and deep surgical wound and limited mobility of the intracranial vessels.

One of the main indications for an IC-IC bypass is the presence of a complex cerebral aneurysm, surgical treatment of which in most cases, as mentioned above, can not be limited to conventional clipping or endovascular surgery only.
Fig. 1. CT and CT angiography scans of the brain of a 59-years-old patient K. at admission.

a — CT of the brain (axial slices): pronounced basal and convexity SAH, intraventricular hemorrhage in the posterior horns of both lateral ventricles, an intracranial hematoma in the right temporal lobe, 7 cm³ in size; b—d — 2D (b) and 3D (c, d) CT angiograms of the brain: the white arrow indicates a large aneurysm (20×14 mm) of the right MCA, blue arrows indicate afferent (M1 segment) and efferent (main M2 segment) vessels located at an acute angle to each other, the red arrow indicates a second hypoplastic M2 segment.

There is no conventional classification of IC-IC bypasses used for treatment of complex aneurysms. This is due to the fact that combinations of various anatomical characteristics of complex aneurysms are extremely diverse, and each case is considered individually and sometimes requires making non-trivial solutions.

Some neurosurgeons with extensive experience in IC-IC bypasses try to develop their classification based on a large number of observations [1, 2, 10, 11, 18]. However, most publications on this topic describe treatment of only one or a few patients who underwent an IC-IC bypass surgery.

At present, the most complete classification is proposed by M. Lawton [3, 14] whose personal experience is based on revascularization surgeries performed in 82 patients in the period between 1997 and 2007 [3]; out of these, 47 patients underwent EC-IC surgery, and 35 patients underwent IC-IC bypass surgery.

Based on his own observations, M. Lawton [3] distinguishes four IC-IC bypass types:

1) in situ bypass: implementation of this bypass requires the donor and recipient arteries to be in the close proximity to each other and to lie in parallel. The author identifies several fragments of the arterial circle of Willis...
Fig. 2. Intraoperative images and a surgery diagram.
a — a hypoplastic M2 segment of the right MCA, originating from the aneurysm body (1); the M1 segment of the right MCA (2); the main M2 segment originating from the aneurysm neck and forming an acute angle with the afferent M1 segment (3); the aneurysm body (4); b — excision of the aneurysm body; the arrow indicates an aneurysm stump; c — implementation of an end-to-end IC-IC bypass between the M1 (1) and main M2 (2) segments of the right MCA after excision of the aneurysm body and transection of the hypoplastic M2 segment; d — the IC-IC bypass (indicated by the arrow); e — a surgical wound after placement of two anastomoses: IC-IC (1); EICMA between the frontal branch of the STA and the right cortical branch of the right MCA on the frontal lobe surface (2).

See continuation of Figure 2 on the next page.
Fig. 2. Intraoperative images and a surgery diagram (continued).

f — a surgery diagram: a MCA aneurysm (1); aneurysm excision (2); a view of the surgical wound with two formed anastomoses (3). A — an aneurysm, M1 — the M1 segment of the right MCA, M2f — the M2 segment (frontal trunk) of the right MCA, M2t — the M2 segment (temporal trunk) of the right MCA, IC-IC, EICMA — see the text, f.l. — the frontal lobe, t.l. — the temporal lobe; g — detection of LBFV via the IC-IC bypass (indicated by the arrow); h — detection of LBFV via the EICMA (indicated by the arrow).
Fig. 3. Postoperative CT and CT angiography scans of the brain one day after surgery and the patient’s appearance 10 days after surgery.

a — a brain CT scan (axial view): ischemic changes in the right frontal and temporal lobes, 21 cm³ in size (in the oval); b—d — 3D (b) and 2D (c, d) CT angiograms of the brain, the red arrow indicates a functioning EICMA, the white arrow indicates a reanastomosis between M1 and M2 segments (the artery caliber in this area is 2.4 mm); e, f — the patient’s appearance 10 days after surgery.
where relative artery positions meet the above requirements: bilateral ACAs (A3 and A4 segments) in the interhemispheric fissure where they turn around the genu and rostrum of the corpus callosum; the MCA branches in the lateral cerebral fissure; the PCA (P2 and P3 segments) and superior cerebellar artery (SCA) in the cisterna ambiens; the bilateral PICAs in the cisterna magna, in the area where two loops of the opposite PICAs lie close to each other under the cerebellar tonsils, anteriorly to the medulla oblongata. This revascularization surgery requires placement of one side-to-side bypass;

2) reimplantation includes dissection of a significant artery originating from the aneurysm and subsequent reimplantation of the artery onto the parent or adjacent artery using an end-to-side anastomosis. This technique is most suitable for complex MCA, ACA, and PICA aneurysms;

3) reanastomosis includes excision of the aneurysm with a fragment of the parent artery and subsequent rejoining afferent and efferent ends of the parent artery with an end-to-end anastomosis. This anastomosis is suitable for treatment of small and medium fusiform aneurysms, when ends of the parent artery can be reconnected with small tension. In the case of complex intracranial bifurcation aneurysms, this technique is used less frequently, given the presence of two or more efferent arteries. In this situation, the first efferent branch should be reanastomosed to the afferent end of the parent artery, and the second (or more) branch should be reimplanted or bypassed with an EC-IC anastomosis;

4) anastomosis with a short interposition arterial bypass is used to connect the donor and recipient arteries for any aneurysm location; the anastomosis can be used as a reanastomosis option when the afferent and efferent ends of the parent artery, after aneurysm excision, can not be reconnected without significant tension.

This surgery involves at least two anastomoses of a different configuration (end-to-end, end-to-side, and side-to-side); this anastomosis is used for different aneurysm locations. A bypass can be harvested from the STA [12, 13, 20], radial artery [19], occipital artery [15], or superior thyroid artery [15, 20], especially in reimplantation of significant arteries of a small caliber (e.g., the M3 segment of the MCA, PICA, or AICA).

However, even this classification does not cover all types of revascularization interventions that can be performed in patients with complex aneurysms. There is a category of surgical interventions that are not formally referred to as anastomoses but are used for reconstruction of intracranial arteries and, therefore, can also be addressed in terms of intracranial revascularization surgery. These interventions include direct reconstruction of an arterial wall defect caused by aneurysm excision using primary sutures or a patch, which were described by L. Sekhar [1, 15, 19, 21].

L. Sekhar who has extensive experience with IC-IC bypasses [1, 10, 15, 19, 20] distinguishes the following types of them, depending on an used microsurgical technique [15]: side-to-side anastomoses (in situ anastomoses in the classification by M. Lawton); direct arterial reconstruction (reanastomosis in the classification by M. Lawton) or reconstruction of a parent artery using an interposition vascular bypass (the fourth IC-IC bypass type in the classification by M. Lawton); reimplantation of significant branches directly or using an interposition vascular bypass (the second IC-IC bypass type in the classification by M. Lawton); direct reconstruction of an arterial wall defect caused by aneurysm excision using primary sutures or a patch.

L. Sekhar et al. [15, 19] also reported cases of combined use of various IC-IC bypasses or combination of IC-IC and EC-IC bypasses when the patient underwent high-flow EC-IC surgery at the first stage, followed by IC-IC surgery with an interposition vascular bypass between a significant artery originating from the aneurysm and the first bypass (double bypass technique).

In the presented clinical case, exclusion of the aneurysm from the circulation through its excision followed by reanastomosis of M1 to dominant M2 segments of the right MCA was considered still during the preoperative planning. During the preoperative preparation, we practiced variants of end-to-end and end-to-side anastomoses between MCA branches using anatomic specimens.

However, the final decision about a revascularization option was made intraoperatively, after revision of the aneurysm and identification of its anatomical features. Given the close proximity of afferent and efferent vessels and the absence of tension upon their apposition, we performed an IC-IC reanastomosis. Given the anatomical features of the right MCA, hypoplasia of the second M2 segment of the right MCA, and intraoperative transection of significant branches extending to the frontal lobe surface, the second surgical stage included (to prevent ischemic injury to the right frontal lobe) an EICMA between the frontal branch of the right STA (the parietal branch was hypoplastic, its caliber was 0.8 mm) and the cortical branch of the right MCA on the frontal lobe surface.

Revascularization surgery is a sought-after trend in surgery of complex brain aneurysms because it enables efficient exclusion of the aneurysm from the circulation and prevents development of ischemic intracranial injuries in the parent artery territory.

Authors declare no conflict of interest.
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Commentary

The article is devoted to the topical problem of vascular neurosurgery — treatment of fusiform aneurysms of the middle cerebral artery using intra-intracranial and extra-intracranial anastomoses.

The case is well described and illustrated by the authors, which certainly should be interesting to a neurosurgical audience.

In our opinion, the general treatment approach in the preoperative stage, after placement of an intra-intracranial anastomosis? This very approach was demonstrated in the presented case.

Microsurgical revascularization interventions should certainly be available in the arsenal of techniques at clinics specialized in the treatment of vascular intracranial diseases because modern reconstructive endovascular surgery can not fully manage complex intracranial aneurysms, especially when the middle cerebral arteries are affected.
An Anastomosis Between the Internal Carotid and Vertebral Arteries in the Treatment of a Patient with Bilateral Carotid Arteries Occlusions

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The article presents a case of successful surgical treatment of a patient with progressive chronic cerebral ischemia due to occlusions of both internal carotid arteries combined with occlusion of the vertebral artery in the first and second segments. We describe a surgical technique that includes an auto arterial carotid-subclavian bypass in the third segment of the vertebral artery, with an extracranial portion of the occluded internal carotid artery (after preliminary thromboendarterectomy) being used as a shunt. Previously, the patient had undergone surgery for creating bilateral EICMA. We analyzed the indications for each phase of the surgery taking into account the peculiarities of compensatory collateral circulation and possible complications of the surgical treatment.

**Keywords:** cerebral artery occlusion, cerebral revascularization, chronic cerebral ischemia.

**Abbreviations**
ICA — internal carotid artery
PCA — posterior cerebral artery
LBFV — linear blood flow velocity
ECA — external carotid artery
CCA — common carotid artery
VA — vertebral artery
ACA — anterior communicating artery
TCD — transcranial Doppler ultrasonography
MCA — middle cerebral artery
EICMA — extra-intracranial microvascular anastomosis

Occlusions of brachycephalic arteries are among the leading causes of ischemic stroke and progressive course of chronic cerebral ischemia. This is especially true in relation to bilateral lesions of both carotid systems, which are characterized by 52% mortality in the acute period [1]. The incidence of bilateral occlusion of the ICA in patients with chronic cerebral ischemia is relatively low and amounts to only 0.5% of the total number of diagnostic ultrasound examinations [2]. Nevertheless, in this group of patients, there are 20% of cases with unstable clinical course in the form of transient cerebral circulation disorders, with the incidence of recurrent ischemic stroke reaching 13% per year [3, 4]. There have also been cases of progression of cognitive and mnestic impairment leading to the development of vascular dementia [5]. Atherosclerotic lesion of the ICA in these patients can be accompanied by stenotic and occlusive lesions of the vertebrobasilar arterial system, which significantly increase the risk of unstable course of chronic cerebral ischemia [3]. This explains the obvious requirement for the surgical treatment of these patients aimed both at revascularization of occluded ICA systems and improvement of the natural collateral circulation at the level of the cerebral arterial circle.

The article presents an example of staged surgical treatment of a patient with bilateral ICA occlusions and occlusion of one of the vertebral arteries in the first and second segments (V1 and V2) developed in the follow-up period. Surgeries on EICMA creation on two sides as well as a rare surgery, carotid-vertebral artery bypass in the V3 segment, were carried out in the course of treatment. In addition, a special modification of this surgical intervention, which takes into account ICA occlusions, was performed.

**Clinical observation**

Patient K., 64 years old, was treated at the Institute of Neurosurgery n. a. Acad. N.N. Burdenko in June and October 2014 and April 2015.

Upon the first admission, the patient complained of weakness in the right limbs, speech impairment, increasing headache and dizziness, recurrent sudden falls on the basis of orthostatic load. The medical history showed that the patient suffered ischemic stroke in the left ICA system with the development of right-sided hemiparesis of up to 3 points and elements of motor aphasia in March 2014. The symptoms partially regressed on the background of conservative treatment. However, manifestations of vertebrobasilar insufficiency in the form of severe dizziness, unsteadiness of gait, syncope on
the background of orthostatic load have soon appeared. Speech disturbances increased, the patient became lethargic. Upon admission, the neurological deficit according to the NIHSS scale was estimated as 7 points. Among comorbidities observed in the patient, there were hypertension II degree, risk 4, chronic bronchitis without exacerbation and hypertrophic cardiomyopathy. The patient is a long-time smoker. Ultrasound examination revealed post-thrombotic occlusions of both ICA, hypoplasia of the right VA, hemodynamic dominance of the left VA. No hemodynamically significant dyscirculation was observed in the vertebral artery system. According to TCD, the blood flow is of collateral type in both MCA. Reduced blood flow in both MCA, which was more pronounced on the left side. Reduced cerebrovascular reserves on the right side and exhausted reserves on the left: LBFV was 55/55 and 45/40 cm/s in the right and left MCA, respectively. Blood flow was symmetric and of normal type in both PCA, LBFV was up to 70—75 cm/s. Taking into account the signs of severe cerebrovascular insufficiency caused by bilateral occlusion of the ICA, surgeries on EICMA creation on the both sides were proposed to the patient. The surgery on EICMA creation between parietal branch of the ACA and cortical (angular) branch of the MCA on the left side was performed on June 17, 2014. The surgery was performed according to the standard procedure. Postoperative period was uneventful. After surgery, the patient noted the improvement in general condition, increased strength in the right leg and improved fine motor skills in the right hand. He became more active. Speech was improved in the form of increased active vocabulary. The degree of neurological deficit was 4 points by NIHSS scale. According to the control ultrasound examination, left EICMA was functioning, its diameter was up to 1.3 mm, volumetric blood flow was up to 65 ml/min.

The patient was readmitted to the Institute of Neurosurgery in October 2014 for the second phase of surgery. The clinical picture showed syncope, unsteadiness of gait, dizziness, and focal hemispheric symptoms. Neurological deficit was 3—4 points by NIHSS scale. According to the ultrasound data, an increase in the volumetric blood flow in the left EICMA of up to 90 ml/min was noted, its diameter was 1.5 mm. The surgery on EICMA creation between parietal branch of the ACA and cortical (angular) branch of the MCA on the right side was performed on October 28, 2014. Decreased syncope and headache were noted in the postoperative period. However, rotatory vertigo remained. Focal hemispheric neurological symptoms were without noticeable dynamics. Control ultrasound examination showed functioning of both EICMA, blood flow velocity in them was up to 80—90 on the left side and 45—50 ml/min on the right side. The patient was discharged under the supervision of a neurologist on a residence.

In April 2015, the patient showed complaints of deterioration in the next follow-up. Neurological examination demonstrated increased right hemiparesis (rate: 3—4 points), limp during walking and severe ataxia appeared. Impaired speech occurred again: it became slow, the vocabulary was impoverished. The value of neurological deficit was 5—6 points by NIHSS scale. There was a suspected occlusion of the right VA in V1 and V2 segments according to the ultrasound data. TCD revealed reduced LBFV in the MCA to 40—45 cm/s on the left side and 50—55 cm/s on the right side, reduction to 50 cm/s in the PCA. SCT angiography was conducted, which confirmed occlusion of the right VA up to the V3 segment. V4 segment of the right VA is filled through hypertrophied deep artery of the neck. Retrograde filling of the right VA was noted (Fig. 1a).

In order to improve the cerebral blood flow, a carotid-subclavian bypass in the V3 segment of the right VA using a fragment of occluded right ICA was proposed.

Thromboendarterectomy from the ICA, bifurcations of the CCA, and auto arterial carotid-V3-subclavian bypass on the right side were performed on April 8, 2015.

Here we describe the surgical intervention. An access to the neurovascular bundle was performed in the linear skin incision (9 cm) along the medial edge of sternoclavicular mastoid muscle on the right side. CCA, ECA and thrombosed ICA were isolated and sutured. Anterolateral access to the V3 segment of the right VA was performed along the medial edge of sternoclavicular mastoid muscle on the right side lateral to the right jugular vein. The accessory nerve was mobilized and relocated on access. Right VA in the V3 segment (between CII and CIII vertebrae) of 1/5 cm long was isolated following dissection of the deep muscles of the neck and coagulation of the venous plexus. CII root on the right side was preserved: it was mobilized and relocated towards CII vertebral arch (Fig. 2a). Vertebral artery was up to 3.5 mm in diameter, weak pulsation was present. After systemic heparinization (2500 u of Heparin i.v.), vascular clamps were imposed on the CCA, ECA and the superior thyroid artery. ICA was excluded from CCA bifurcation. A heterogeneous dense atherosclerotic plaque with the decay turning into a widespread blood clot was found in the mouth of the ICA. ICA was dissected longitudinally in 0.5 cm distally. Eversion endarterectomy from the ICA mouth (5.5 cm) was performed. However, retrograde blood flow was not achieved (see Fig. 2b). Homogeneous dense atherosclerotic plaque extended to the CCA bifurcation narrowing the latter up to 50% and proximally for over 3.5 cm. CCA was further dissected proximally in 1.5 cm. Open carotid endarterectomy from the CCA bifurcation (3.5 cm) and the mouth of ECA (1 cm).

A circular continuous suture between the ICA and CCA bifurcation was imposed with Prolene 6.0 thread. Next, a clamp was applied at ICA immediately
distal to anastomosis, the clamps from the upper thyroid artery, ECA and CCA were removed. Good pulsation of the CCA, ECA and thyroid artery was achieved in the wound. No bleeding from the area of vascular suture was observed. ICA was tied and cut off 4.5 cm distal to the mouth (see Fig. 2c). Hydraulic dilation of the ICA and its dissection in the proximal direction were conducted. Next, clamps were imposed on the V3 segment of the VA, it was crossed at the level of the proximal clamp; proximal end of the artery was coagulated. The lumen of the vertebral artery was free from clots. An end-to-end anastomosis between the ICA and the V3 segment of the vertebral artery in the distal direction was imposed. The clamps were removed from the arteries; good pulsation of the arteries in the wound was achieved (see Fig. 2d).

Homeostasis. Layered sutures were imposed on muscles and subcutaneous tissue. Intradermal suture to the active drainage in the vascular suture zone was imposed. A bandage was applied. Arterial clamping time was 30 minutes. Increased symptoms of vertebrobasilar insufficiency in the form of enhanced dizziness and orthostatic insufficiency were noted in the patient in the postoperative period. Slight tremor of hands appeared. At the same time, the patient became noticeably more active again, the speech improved, right hemiparesis partly regressed to 1—2 points. Neurological deficit amounted to 3—4 points by NIHSS scale. Increased vertebrobasilar symptoms were considered as manifestation of the syndrome of cerebral hyperperfusion in the vertebral artery system. This was confirmed by increased LBFV of 60—65 and 85—90 cm/s in the MCA and PCA, respectively. Rheological and metabolic therapy and strict monitoring of the systemic blood pressure with maintaining of the systolic blood pressure at the level of not less than 120 mmHg were conducted. The symptoms persisted during the first 3—4 days and then significantly regressed. The level of neurological deficit was 3 points by NIHSS scale at discharge. Control ultrasound and SCT angiography confirmed good functioning of carotid-spinal shunt. Volumetric blood flow was 187 ml/min in it.

Control ultrasound examination after 6 months confirmed good functioning of carotid-vertebral bypass with the value of volumetric blood flow of up to 230 ml/min. The signs of vertebrobasilar insufficiency and syncopal episodes completely regressed in the clinic. Slight paresis of the right hand (more in the arm) with a reduced strength and violation of fine motor skills (within the range of 1—2 points) remained. The patient speaks freely and quickly, expresses thoughts clearly. In general, the degree of social adaptation increased: the patient returned to the previous professional activity. Neurological deficit was 2—3 and 1 points by NIHSS and Rankin scales, respectively.

**Discussion**

The current clinical case illustrates the importance of cerebral perfusion restoration in patients with the consequences of ischemic stroke and signs of persistent chronic cerebral ischemia. A major role in this is played...
by the vertebrobasilar arterial system, especially in patients with well-developed posterior parts of the circle of Willis [6]. Compensation of cerebral blood flow in the system of asymptomatic ICA occlusion is known to be due to the vertebral arteries in 45.4% of cases and due to the opposite ICA in 9.1% of cases. While in other cases (45.5%), there are two arterial systems involved in blood flow compensation [7]. This fact can explain a significant increase in hemispheric symptoms in our patient after development of post-thrombotic occlusion of the right VA. At the same time, the possibilities of EICMA, as this observation demonstrates, does not allow full compensation of the perfusion deficit caused by a decrease in collateral blood flow from the vertebral artery system.

In this case, the surgery of carotid-vertebral bypass allowed effective compensation for cerebral blood flow deficiency and led to regression of both the existing hemispheric neurologic symptom and vertebrobasilar insufficiency.

First neovascularization of the V3 segment of VA in patients with carotid artery occlusions was described by L. Carney [8] in 1978. The author noted advisability of this surgery in patients with pathology of the VA in the second segment (occlusion, dissection, extravasal compression) in combination with the ICA occlusion and developed posterior communicating arteries. These interventions were further actively used in patients with PA pathology in the second segment both in Russia [9] and abroad [10, 11]. As a rule, autovenous shunts or ECA branches (occipital artery) were used as the donor artery. It should be noted that autovenous shunts are more prone to the development of postoperative thrombosis (flexures, the presence of valves), while the use of ECA branches significantly limited the functional capacity of the created anastomosis [11]. Moreover, the surgery was technically difficult: all of this limited its use as a method of treatment of patients with occlusions of the carotid artery system.

In the analyzed clinical observation of the patient with bilateral ICA occlusions, the posterior segments of
the circle of Willis served as the main source of blood supply of the systems of both MCA, which determined the efficacy of carotid-vertebral artery bypass. Unlike previously described variants of vertebral artery V3 segment revascularization, we used the patient’s ICA as the donor artery after preliminary thromboendarterectomy. The use of a shorter auto arterial shunt in combination with the described sequence of the stages of surgical intervention and favorable hemodynamic conditions for the shunt functioning (VA diameter of more than 3 mm, anastomosis of the end-to-end type, high need for revascularization in the absence of hyperplasia of contralateral VA) enabled stable functioning in the reconstruction area with high values of volumetric blood flow (up to 230 ml/min) during the whole period of the follow-up.

Of special note is the high risk of hyperfusion syndrome in the early postoperative period: especially in patients with multiple steno-occlusive lesions of the brachycephalic arteries, which are characterized by impaired autoregulation of cerebral circulation. In the analyzed clinical observation, cerebral hyperperfusion syndrome was accompanied by a transient increase in vertebrobasilar insufficiency. However, the development of hemodynamic brainstem ischemic stroke or bleeding to the posterior fossa structures could not be excluded. The possibility of such complications should be taken into account when planning revascularization of the V3 segment of the vertebral artery.

**Conclusion**

Revascularization of the third segment of the vertebral artery in patients with concomitant occlusions of the carotid and vertebral arteries on the same side allow improvement of the collateral blood supply to the occluded ICA and can result in regression of hemispheric neurologic symptoms. A fragment of the occluded ICA can be used as a shunt after thromboendarterectomy.

**Authors declare no conflict of interest.**

**REFERENCES**


**Commentary**

In this regard, the work presented by the authors is extremely interesting because it allows practicing neurosurgeons and vascular surgeons to become familiar with the academic approach to the problem of surgical solution in multiple atherosclerotic lesions of the brachycephalic arteries. I am sure that most hospitals in our country and abroad would have denied to the patient in the surgical treatment and would have sent him to neurologists for conservative symptomatic "aftercare" in anticipation of the natural unfavorable outcome of the disease. The authors, however, had enough experience and courage to gradually and purposefully point out the priorities and perform reconstruction of the affected cerebral and brachycephalic arteries and thereby not only prolong life but also socially adapt a severe vascular patient.
Rapid development of vascular surgery for the past six decades has determined a wide range of options of surgical interventions of almost all segments of the brachycephalic arteries. However, despite the fact that there are almost no blind spots left in the surgery of cerebral arteries and the search for new types of reconstruction is quite problematic, the specialists of the Institute of Neurosurgery n. a. Acad. N.N. Burdenko conducted a completely new surgery using an already thrombosed internal carotid artery. Of course, there are various modifications of the surgery of the main arteries of the head involving endarterectomy and movement of the vessel in a different direction, but this type of surgery was probably carried out for the first time.

To date, the cardio-vascular surgeon, professor of Michigan university R. Berger, has the widest experience in the world: he performed more than 250 distal reconstructions of the vertebral arteries. However, he has not carried out such modification. The authors first proposed the use of external (EICMA creation) and internal (placement of distal carotid-vertebral anastomosis) carotid arteries in absolute indications for the surgical treatment.

It is encouraging that the new surgery was performed by neurosurgeons actively dealing with the problems of the surgical treatment of cerebral ischemia. This fact once again underlines the validity of the postulate that neither vascular surgeons nor neurosurgeons have a need to share this field. The realities of the modern life are such that the surgery of brachycephalic arteries is the governmental problem, which requires a multidisciplinary approach and collaboration of various specialists, especially considering the fact of the huge need in the surgeries of the main arteries of the head in our country (up to 100 ths. per year), with only 23 ths. of them being accomplished, provides the necessity to attract more neurosurgical and vascular hospitals for a planned solution to the problem of cerebral stroke by surgical interventions.

I would like to congratulate the authors on the successful clinical observation and, if you want, a beautiful surgery. Acquaintance with their positive experience will be very useful for professionals actively involved in the surgical treatment of acute and chronic cerebrovascular insufficiency.

G.I. Antonov (Moscow, Russia)
The Jannetta procedure is microvascular decompression (MVD) of the trigeminal nerve (TN) root, which involves the use of padding to separate the nerve from a compressing vessel. Fasciae, muscles, cotton, ilavon, and other materials have been used as a pad. Teflon (polytetrafluoroethylene) has been recognized as the material of choice for this surgery because it is very safe, nonresorbable, and least immunogenic [1―3]. However, there are reports of granulomas associated with various surgical procedures using Teflon, which demonstrate that inert Teflon can nevertheless cause a local immune response [4]. The most often giant cell inflammatory responses associated with Teflon applications have been described in orthopedics, maxillofacial surgery, and otolaryngology [5, 6]. Teflon granulomas after MVD occur in both TN neuralgia and hemifacial spasm as well as in their combinations [4, 7―9].

Clinical case

A 63-year-old female patient was admitted to the Federal Center of Neurosurgery with complaints of growing paroxysmal pains, in particular searing pain, in the innervation area of the first and second branches of the left TN in May 2015. Also, left facial numbness was present.

The first attack of TN neuralgia occurred 21 years ago; pain spread around the innervation zone of the second and third branches of the left TN. In 2004, the patient underwent radiofrequency thermal destruction of the sensitive portion of the Gasserian ganglion, which had a short-term effect.

The patient underwent MVD of the left TN root for typical TN neuralgia (type 1 according to K. Burchiel) in May 2014. The intervention was performed with the patient in the park bench position. Retrosigmoid craniectomy, 2 cm in diameter, was performed. The TN root was accessed along the superior edge of the cerebellum, without use of retractors. After coagulation and section of the petrosal vein, we accessed to the TN root. The root was separated from arachnoid adhesions. We found a conflict between the TN root and the superior cerebellar artery (SCA) that was located distally to the root entry zone (REZ) and did not reach the brainstem. Resection of the suprameatal tubercle (petrous endostosis) was performed using a high-speed drill to resolve the neurovascular conflict and mobilize the artery branch. When drilling the suprameatal tubercle, a surgical wax plate was used for protection against bone dust. The remaining bone dust was removed by simultaneous irrigation and aspiration. The TN root was firmly fixed to the SCA wall and separated; the artery was transposed. The artery and the nerve were interposed with Teflon felt pieces. Careful hemostasis and washing of cisternal spaces were performed before placing the Teflon felt. There were no signs of blood impregnation of the Teflon felt.

After surgery, the pain was completely relieved; sensory disorders completely regressed. However, the pain recurred after 11 months.

The neurological status at readmission was as follows: multiple trigger points and patch sensory impairment with areas of hyperpathia in the innervation zone of the first and second branches of the left TN. Pain was scored 10 on the Visual Analog Scale (VAS), 5 on the Barrow Neurological Institute Pain Scale (BNIPS) (strong, intractable pain), 170 on the BPI-facial scale, and 4 on the DN4 scale (neuropathic pain).

Thus, TN neuralgia recurrence in the patient was characterized by a changed pain localization (the first and second branches) compared to the initial pain localization in the innervation zone of the second and third branches of the left TN, emergence of neuropathic pain, and recurrence of facial sensory impairments.

Brain MRI (19.05.2015) revealed asymmetry of the pontine cistern, with decreasing its size on the left. The length of the right TN root was 5.5 mm, and that of the left TN root was 2.5 mm. An oval lesion was visualized

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along the upper contour of the left TN. The lesion had a hypointense signal in the T2-weighted mode, isohypointense signal in the FLAIR mode, and isointense signal in the T1-weighted mode. The TN root was compressed (Fig. 1). Following introduction of a contrast agent, intense agent uptake was observed in the lesion whose size was 8 × 5 × 4 mm. The lesion had clear contours and was closely adjacent to the cerebellar tentorium (Fig. 2).

During re-operation, the left TN root was found to be completely enveloped in Teflon. A rounded lesion was detected in the distal cisternal third of the root, on its outer-upper edge. The lesion was a conglomerate of the Teflon felt and pink scar-altered tissue (Fig. 3). The lesion was resected en bloc; the TN root was freed from adhesions, felt, and saccings almost all throughout its length. A part of the Teflon felt was left on the SCA wall and TN. No signs of neurovascular conflict were found.

Macroscopically, the granuloma appeared as a dense yellowish-gray lesion of an irregular shape.

The surgical specimen was subjected to histological and immunohistochemical studies. The histological study used hematoxylin and eosin staining and Van Gieson staining. The immunohistochemical study was performed in accordance with the recommendations of antibody manufacturers and with the recommendations provided in the guidelines for immunohistochemical studies [10, 11]. Sections were incubated with anti-CD68 antibodies (PG-M1 clone, mouse monoclonal, DAKO, Denmark). A polymer peroxidase detection system (EnVision FLEX, DAKO, Denmark) was used for immunostaining. The final step included hematoxylin staining of cell nuclei.

Microscopy revealed that the lesion consisted of tissue fragments with focal diffuse lymphoid infiltration, single plasma cells and eosinophils, as well as with a large number of macrophages (Fig. 4) located throughout pronounced fibrosis (Fig. 5). The infiltrate comprised a large number of giant multinuclear cells. Numerous voids, some of which contained foreign material in the form of fibers, were detected. There were calcification foci. Positive staining of giant multinuclear cells with CD68 antibodies was observed in the immunohistochemical study (Fig. 6).

According to the histological report, chronic granulomatous inflammation around foreign bodies was diagnosed.

The postoperative period was uneventful. At the time of hospital discharge, the pain and sensory impairments regressed, trigger points were not detected. After surgery, the pain was scored 0 on VAS, BPI-facial, and DN4 and 1 (no pain) on BNIPS.

Discussion

Microvascular decompression is the surgery of choice in patients with TN neuralgia in the presence of an identified neurovascular conflict. The surgery does not damage to the anatomical integrity of the trigeminal nerve root and in most cases is not accompanied by significant neurological losses. In this case, the efficacy of surgery reaches 98% [12, 13]. A 5-year pain recurrence rate is 6—38%, with an average annual increase of 2% [12, 14]. The causes of recurrent neuralgia include insufficient decompression of the TN root, a neurovascular conflict not identified during the first surgery, implant dislocation, recompresion due to vein

Fig. 1. A MRI scan, T2 mode. A hypointense area along the upper contour of the TN root (indicated by arrows).

Fig. 2. Contrast-enhanced MRI, T1-weighted mode. A contrast-uptaking lesion adherent to the cerebellar tentorium.
recanalization, and granuloma development [3, 12, 14, 15].

According to the literature, Teflon granulomas occur in 1.1–7.3% of all MVD cases performed in accordance with the Jannetta procedure [4, 16, 17]. They can cause pain in 13–50% of all recurrent neuralgias [15, 17, 18]. The time from MVD to granuloma-associated pain recurrence ranges from 1 month to 8.5 years; facial pain often recurs within the first 2 years [4, 8, 9, 16, 17].

According to various authors [16, 17], there are no pathognomonic symptoms of Teflon granuloma, but pain in recurrent TN neuralgia often involves new TN branches and is accompanied by facial hypoesthesia. Some authors [9] note that Teflon granulomas are characterized by a gradual increase in symptoms and their severity. A neuropathic component and prolonged pain are not typical of this group of patients [16]. P. Smucker et al. [7] described a case of Teflon granuloma developed 6 years after MVD, which manifested not as pain but as brainstem symptoms.

In most cases, neuroimaging studies enable diagnosis of granuloma that usually appears on a T2-weighted image as a hypointense contrast accumulating area with a mass effect. Granuloma can contain calcifications [8, 9, 16, 17] and appear as a heterogeneous solid or cystic lesion [7]. CT identifies granuloma as a calcified lesion [16]. D. Parmar et al. [9] described a Teflon granuloma that was accompanied by edema in the brainstem and cerebellum. According to P. Smucker et al. [7], granuloma appeared as a multicavity cystic lesion that was located in the cerebellopontine angle and extended to the midbrain.

The diagnosis of Teflon granuloma should be first differentiated from posterior cranial fossa meningioma, VIII nerve neuroma, as well as an aneurysm and rare granulomatous diseases such as sarcoidosis and tuberculosis [19]. According to H. Capelle et al. [16], a normal MRI picture does not exclude the presence of granuloma, which was found using neuroimaging only in 1 out of 3 patients, in whom granuloma was later found during surgery. Teflon granuloma can also lead to false-positive results of glucose PET/CT, which complicates its differential diagnosis from malignant tumors [6]. According to L. Hacein-Bey et al. [20], Teflon granulomas with other localizations can also be indistinguishable from surrounding tissues.

In most cases, it was intraoperatively found that granulomas were connected to the pyramid edge, DM, or tentorium and created a mass effect [16, 17]. On the basis of their observations, Chen et al. supposed that granuloma develops when Teflon contacts the DM, but not the brainstem [17]. The authors also observed the development of granuloma in cases where the SCA was an offending vessel in the first MVD, which might be caused by application of a large amount of Teflon and its...
contact with the DM [17]. They did not observe granulomas in MVD for hemifacial spasm and explained this fact by the use of small Teflon pieces and the absence of contact between the Teflon felt and the DM [17]. According to other authors [4, 7], Teflon granuloma was tightly adherent to the TN REZ or involved the brainstem.

The presence of hemosiderin-loaded macrophages observed in a histological study of granulomas suggests that small intraoperative bleeding into the Teflon felt may induce granuloma formation [16]. Later, after migration of immune cells to foreign material, a chronic granulomatous inflammation with calcification and tumor growth develops [16].

The use of some material for fixation of Teflon as a risk factor for granuloma development remains unclear [16].

A chronic inflammation without signs of bacterial infection is the mechanism of granuloma development [16, 21]. Macroscopically, granuloma appears as a gray-brownish lesion tightly adherent to the nerves, vessels, and DM and exerting a mass effect [16]. Histological studies of granuloma reveal Teflon microfragments, which are surrounded by multinuclear giant cells, and hyalized scar tissue containing collagen, hemosiderin depositions, and microcalcifications [4, 7, 9, 16].

H. Dedo et al. [21] described different stages of Teflon granuloma development. Investigation of specimens sampled 4 weeks after surgery revealed major acute reactions, in which Teflon fibers were surrounded by histiocytes. Fibrous tissue was found in granuloma 3 months after the first surgery, while a large amount of giant cells with Teflon particles in the cytoplasm were detected in the period from 6 months to 3.5 years. In specimens obtained 10 years after surgery, granulomas were capable of growing and preserving the structure similar to that typical of earlier periods.

In many interventions for granulomas, vascular compression is not detected, and surgery is reduced to granuloma resection, neurolysis, and release of the TN REZ [17]. If a neurovascular conflict with the nerve root is detected during surgery, H. Capelle et al. [16] consider placement of a new Teflon felt to be safe because removal of granulomatous masses and adhesions stops inflammation.

According to many authors [16], re-decompression in patients with recurrent TN neuralgia caused by Teflon granuloma yields good outcomes without worsening of symptoms in the postoperative period. Complete regression of sensory impairments was described in some cases [17].

Based on intraoperative findings, researchers recommend isolation of a Teflon felt from the DM to reduce the risk of Teflon granuloma. However, this procedure has not been proven to eliminate the risk of granuloma formation [9, 17]. I. Premsegar et al. [4] suggest wrapping the TN root using Surgicel to isolate Teflon from contact with the nervous tissue. Other authors [2, 22] recommend the maximum abduction of an offending vessel to prevent contact between the Teflon felt and the TN root.

**Conclusion**

Teflon granuloma is a rare complication after MVD of the TN root and can be the cause of pain recurrence at different times after surgery. Diagnosis of granuloma requires application of imaging techniques, in particular contrast-enhanced MRI of the brain that in most cases can detect a contrast enhanced lesion located in the area of previous intervention. If Teflon granuloma is detected, re-operation is indicated. In this case, the surgical approach should be aimed at granuloma resection, neurolysis, and elimination of a neurovascular conflict, if present. Careful intraoperative hemostasis is required to prevent blood impregnation of a Teflon felt, which reduces the risk of Teflon granuloma formation after surgery.

**Authors declare no conflict of interest.**
A growing number of neurologists and neurosurgeons engaged in treatment of trigeminal neuralgia turn to vascular decompression of the trigeminal nerve, considering it as the only pathogenetic treatment for this pathology. In this regard, extension of the knowledge about possible effects of this widely used surgery is very important, and topicality of the presented article is beyond a shadow of a doubt.

Competently performed vascular decompression of the trigeminal nerve results in disappearance of pain in almost all operated patients, but pain can recur in some cases. Pain recurrence may be caused by Teflon-granuloma.

Development of Teflon granuloma in the postoperative period is a rare complication of vascular decompression of the trigeminal nerve root, which is almost always the cause of pain recurrence at different times after surgery. Causes of Teflon-associated granuloma are still unknown. The main cause is supposed to be intraoperative bleeding into the implant area, a large amount of implant material, the intimate location of the implant to the cerebellar tentorium, and autoimmune diseases of the patient. Our experience demonstrates that only hemorrhagic impregnation of the felt may be a trigger in the development of inflammatory reactions at the junction of the trigeminal nerve and the brainstem. However, our practice (more than 500 vascular decompressions for trigeminal neuralgia) has had no case of granuloma formation at the felt site. It is difficult to decide if this fact is related to the economical use of synthetic implant materials or to preservation of the felt in a large amount of implant material, the intimate location of the implant to the cerebellar tentorium, and autoimmune diseases of the patient. Our experience demonstrates that only hemorrhagic impregnation of the felt may be a trigger in the development of inflammatory reactions at the junction of the trigeminal nerve and the brainstem. However, our practice (more than 500 vascular decompressions for trigeminal neuralgia) has had no case of granuloma formation at the felt site. It is difficult to decide if this fact is related to the economical use of synthetic implant materials or to preservation of the felt in a "pure", i.e. blood-free, condition. In any case, these two circumstances make it possible to reduce and probably avoid granuloma formation after vascular decompression of the trigeminal nerve.

V.N. Shimanskiy (Moscow, Russia)
Paradoxical Air Embolism Resulted in Acute Myocardial Infarction and Massive Ischemic Brain Injury in a Patient Operated on in A Sitting Position


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Paradoxical air embolism (PAE) is a rare life-threatening complication when air emboli enter arteries of the systemic circulation and cause their occlusion. Here, we describe a clinical case of PAE developed during neurosurgery in a patient in the sitting position. PAE led to injuries to the cerebral blood vessels, coronary arteries, and lungs, which caused death of the patient. An effective measure for preventing PAE is abandoning surgery in the sitting position in favor of surgery in the prone position.

Keywords: neurosurgery, sitting position, paradoxical air embolism, ischemic brain injury, acute myocardial infarction.

Abbreviations

BP – blood pressure
VVE – venous air embolism
ICA – internal carotid artery
ALV – artificial lung ventilation
PMA – potassium-magnesium asparaginate
t – computed tomography
CK – creatine kinase
LDH – lactate dehydrogenase
LV – left ventricle
LBFV – linear blood flow velocity
ECA – external carotid artery
ARDS – acute respiratory distress syndrome
CCA – common carotid artery
VA – vertebral artery

Paradoxical air embolism is a rare but potentially serious, life-threatening complication when air emboli enter arteries of the systemic circulation from the right heart and pulmonary artery and cause their occlusion. In neurosurgical practice, PAE has been most frequently observed during operations in the sitting position or elevated head end position as a secondary complication of venous air embolism [1–4]. Intracardiac shunting through a patent oval window is the most common cause of PAE, however, paradoxical embolism during anesthesia may also be caused by intrapulmonary arteriovenous shunts [5, 6]. These air emboli potentially can enter any arterial vessels, but they are often found in the brain vessels (branches of middle cerebral artery) [1, 2]. However, in our clinical case, PAE led to not only cerebral circulation disorder, but also coronary circulation disorder and acute myocardial infarction.

Clinical case. A 48-year-old man admitted in the Institute of Neurosurgery with the diagnosis of astrocytoma of the medulla oblongata and cholesteroloma of the left cerebellopontine angle to perform an open biopsy of the medulla tumor under neurophysiological monitoring. At the pre-hospital stage, we performed the following investigations: ECG, EEG, US scanning of lower extremity veins, clinical and biochemical blood test and urine analysis. No disturbances were detected.

In the operating room, the patient was carried out a routine monitoring, including three-channel ECG, invasive blood pressure measurement and pulse oximetry (SpO₂). After induction of anesthesia (propofol + fentanyl + rocuronium), we performed orotracheal intubation without any technical difficulties, then we measured end tidal carbon dioxide (EtCO₂). ALV was carried out in the controlled mechanical ventilation mode (CMV), RMV=6.0 L/min, RR=14, fraction of inspired oxygen 35%. The right jugular vein was punctured and catheterized with a triple lumen catheter without any technical difficulties. The position of

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During the first 12 hours after the operation, this patient demonstrated the increase in cerebral and focal neurological symptoms. There was no response to addressed speech, pain and jet stimulation of face. For passive lifting eyelids, there were gaze fixation symptom and bilateral mydriasis without photoreaction. Corneal, oculocephalic and cough reflexes are absent. There were muscle atonia and areflexia. We observed a tendency to hypotension despite increasing doses of norepinephrine maximum of 5 mg/kg/min. Repeated CT scan within 12 hours after operation revealed diffuse cerebral edema with no gray/white matter differentiation and pneumocephalus (Fig. 5).

In the first postoperative day, the patient’s condition has not improved, with diffuse muscle atonia, areflexia and hypotension during the treatment with high doses of norepinephrine. According to biochemical blood analysis, CK was 845 (N<200 U/L), LDH 665 U/L (N=100—190 U/L), troponin 18.76 (N<0.1 μg/L). In Doppler scanning, Willis circle arteries are not visualized. Color Doppler imaging demonstrated spontaneous staining of the neck arteries (CCA, ICA, ECA and VA), LBFV=20 cm/s. Repeated echocardiography found the following parameters: EF 31—33%, CI=2.6 L/min·m², and increased LV. The additional echocardiography changes included a significant reduction in local LV contractility and aneurysm in the top and mid-ventricular with thrombotic masses, which were not tightly fixed and occupied almost the entire top, and a significant decrease in pumping function.

Subsequently, the patient’s condition was extremely difficult and corresponding to atonic coma; normal hemodynamic parameters were maintained with only a continuous infusion of norepinephrine using the maximum dose. On the 12th day of stay in the intensive care unit, the patient died; his death was associated with increasing cardiovascular insufficiency. An autopsy was not made at the insistence of his relatives.

**Discussion**

This article describes a rare clinical case of paradoxical air embolism affected cerebral and coronary arteries and lungs. In literature, we have found only a few similar observations. However, it should be noted that all cases of coronary air embolism were characterized by echocardiogram changes and hemodynamic instability, which regressed in a short time (within 30 min) after infusion and inotropic therapy. Furthermore, air emboli mainly entered the right coronary artery [7, 8].

Venous air embolism is a common complication of neurosurgery in the sitting position [2, 4, 9—12]. According to different authors [1—3, 5, 11, 13], the incidence of this complication ranges 1.6—76%, depending on whether some episode of VAE was reported by authors (all cases or only massive), and used...
diagnostic methods, which have different sensitivity. The lung is the main target organ in air embolism. The severity of lung injury varies from asymptomatic to ARDS [1, 2]. A patent oval window or pulmonary shunt are factors that predispose to air entry in systemic circulation [1, 2, 6, 14]. This may cause ischemic damage of any organs, however, more common target organs were brain, skin and myocardium [1, 2, 5]. According to different authors (primarily sectional study of random unselected deaths for various reasons), the frequency of patent oval window is 5-13% of the overall population [3, 5, 13, 15]. Preoperative examination, including transthoracic Doppler with Valsalva test and contrast enhancement did not allow identifying this anomaly in 1/3—1/2 of the patients [16]. Firstly, transthoracic Doppler method is not sensitive enough to detect patent oval window; secondly, in some cases, the oval window starts to work only in conditions of high intrathoracic pressure during ALV. This situation is particularly exacerbated by development of VAE, as there is increased pressure in the right ventricle due to massive air entry in the pulmonary capillaries leading to increased pressure in the pulmonary circulation and the opening of the oval window. This information is clinically significant in terms of PAE prevention: 1) we can’t identify a functioning oval window in all cases even using transesophageal EchoCG; 2) it is impossible to identify functioning vascular anastomoses between the pulmonary artery and bronchial arteries, which are responsible for deaths due to PAE with no septal defects [17].

Currently, there are no specific methods for the treatment of lung damage caused by venous air embolism. There are a number of works that show the effectiveness of hyperbaric oxygen therapy in patients with VAE. It should be noted that this therapy was used in scuba divers with caisson disease due to violations of surfacing technique which was accompanied by the appearance of nitrogen bubbles in the blood [18, 19]. There is evidence of the effectiveness of ALV 100% for nitrogen removal and thus reducing the amount of air bubbles [20]. Overall, the treatment of VAE is symptomatic and aimed to organ failure correction. The lung damage due to VAE often

**Fig. 1. Patient’s ECG recorded intraoperatively.**
Sinus rhythm, horizontal ECA. ST-segment elevation in V1—V5, abnormal QS wave in V1—V2.
Fig. 2. Patient’s ECG prior to surgery. Without pathological findings.

Fig. 3. Chest X-ray, anteroposterior view. Mediastinal shadow is not displaced. A marked diffuse decrease in pulmonary tissue transparency as ground glass opacity.

corresponds to a classic ARDS [19, 21]. In these cases, according to the open lung concept, breathing support was performed, including recruitment maneuver using adequate PEEP. PAE due to a patent oval window or pulmonary shunt may cause the development of multiple organ failure which required an appropriate and intensive therapy [22]. Brain damage during PAE determines the need for neuroprotection. One of the most effective methods of neuroprotection is retrograde cerebral perfusion and cerebral or systemic hypothermia; however, the effectiveness of this technique in patients with paradoxical air embolism is currently poorly known [12, 23, 24]. Coronary air embolism may lead to myocardial infarction, which is indistinguishable from myocardial infarction due to atherothrombosis in clinical and laboratory characteristics. However, considering the absence of coronary thrombosis, treatment approaches for acute myocardial infarction due to PAE differ from accepted standards for management of patients with acute coronary syndrome. Obviously, fibrinolytic, antiplatelet and anticoagulant therapy is not effective in these patients, and even dangerous because of risk of intracranial bleeding complications in the early postoperative period. The main therapeutic options are
Fig. 4. CT scan of the brain performed immediately after surgery.
Pronounced pneumocephalus.

Fig. 5. CT scan of the brain performed 12 h after surgery.
Pronounced cerebral edema with signs of lateral dislocation. Residual pneumocephalus. Reduced gray/white matter differentiation.
correction of central hemodynamics and inotropic support, if necessary, [25]. Also, it seems appropriate to prescribe β-blockers primarily providing elongation of diastole and improved coronary perfusion, and secondly, reducing myocardial oxygen demand and the necrotic zone.

The absence of specific treatment of venous air embolism and PAE, and the severity of disease underline the importance of prevention. According to some authors [2, 14, 16, 26, 27], transoesophageal echocardiography during surgery allow detecting and preventing the development of venous air embolism in patients at risk. Transoesophageal sensor was placed and fixed in such way that you can see superior vena cava, right atrium and LV in the sitting position of patient; it would allow timely identification of air microbubbles in the blood. Also, this intraoperative method allows evaluating a function of the patent oval window that theoretically will reduce the risk of venous and paradoxical air embolism [2, 16]. However, the difficulty of this argument was discussed above.

The method of air embolus evacuation from the right heart through a special multiple lumen catheter designed by Bunegin and Albin is highly effective in VAE. However, a correct insertion of the aspiration catheter is not a simple procedure to be carried out under X-ray control. [28]

Certainly, the methods of VAE prevention in neurosurgical patients operating on in the sitting position allow reducing the frequency of PAE. Thus, it is believed that surgery in a half-sitting position with raised foot-end of the operating table designed by S. Jadik and et al. reduces the risk of VAE [29]. In this position, the hip joints are flexed to a maximum of 90°, legs are raised upwards so that the patient’s feet are above his head. The body of patient is maximum reflexed, his head is deflected and fixed upfront. For this head position, it is necessary to control a sufficient space for compression of jugular veins. This position also reduces the risk of VAE providing by increased pressure in the right atrium. This is not the only publication where authors try to avoid negative intrasinusal pressure by the rise of lower extremities, forced infusion therapy with colloid solutions and other tricks [30]. In one work, it has been offer to use special pneumatic compression pants (‘military antishock trousers’), which squeezed the deposited blood out of lower extremity vessels [31]. The problem of these preventive approaches is very limited benefit and their preventive effect was not confirmed by robust studies [1, 2].

Formally, there are three causes of VAE in neurosurgical patients operated on in the sitting position: 1) the injury of sinus walls and large cerebral veins during trepanation using this surgical approach (almost unavoidable situation); 2) the absence of any protective mechanism for collapse of damaged veins and sinuses due to the rigidity of their walls (the mechanism described for peripheral veins); 3) the negative pressure in the brain cerebral veins and sinuses due to postural circulatory reactions [1, 2]. The last cause is the only one which may be really affected by several ways [32].

1. Positive end expiratory pressure. Unfortunately, this method proved to be not only ineffective, but also dangerous. At high PEEP, the effect on intrasinusal pressure appeared to be inverse, i.e. reduced effect is probably due to a decrease in the cerebral blood flow [32]. One study using contrast echocardiography demonstrated that PEEP contributes to air embolus displacement from right to left side, thereby increasing the risk of PAE [33].

2. Inflatable neck tourniquet. This simple device allows increasing intrasinusal pressure above the atmospheric due to external compression of jugular veins [34]. It is 100% effective but time-consuming method, as for safety reasons it requires catheterization of the jugular vein (venous pressure control) above the tourniquet position. [32]

3. Controlled moderate hypercapnia. This method was first described by a group of German authors in 1991 [35] and also proved to be highly efficient as well as easy to implement [32].

However, the most effective measure for preventing VAE in neurosurgical patients is abandoning surgery in the sitting position in favor of surgery in the prone position [36].

Conclusion

Thus, venous air embolism in patients with a patent oval window or intrapulmonary shunt is a rare but really life-threatening complication of neurosurgery in the sitting position. Effective measures for preventing venous air embolism can reduce the risk of paradoxical embolism, and the most effective one is abandoning surgery in the sitting position in favor of surgery in the prone position.

Authors declare no conflict of interest.
REFERENCES


Commentary

The team of authors has reported a clinical case of venous and paradoxical air embolism in the patient with brain stem tumor. It is very threatening and sometimes fatal complication of neurosurgery in the sitting position. This article discusses different approaches and methods published previously by domestic and foreign researchers for preventing the development of air embolism complications and their treatment. We discuss algorithms of pre- and intraoperative patient examination and management. During the discussion of this clinical case, the authors has reported the literature data on the possible causes of venous and paradoxical air embolism in neurosurgical practice.

In present clinical case, paradoxical air embolism that developed during neurosurgery in the sitting position led to acute myocardial infarction and stroke, which eventually caused the patient’s death. The authors focus on pre- and intraoperative detection of these complications, indicating that effective treatment of venous and paradoxical air embolism is not currently developed. The authors indicate the need for neurosurgery in the prone position in any technically possible case, and the maximum abandoning surgery in the sitting position to reduce the risk of air embolism complications.

The article may be useful not only for neurosurgeons and anaesthetists, but also any related specialist participating in the treatment of patients with brain damage.

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Intracranial hemorrhage is the most severe complication of traumatic brain injury (TBI), which occurs in 3—50% of TBI patients (depending on the severity of the injury) [1, 2]. Without an effective surgical treatment, massive intracranial hemorrhages worsen prognosis from favorable to disability and even death. Moreover, late and/or inefficient diagnostic procedures lead to similar worsening of injury outcomes [3—28].

Surgical treatment of acute epidural hematoma

In the case of epidural hematoma larger than 30 cm³, surgical intervention is required regardless of the degree of consciousness depression on Glasgow Coma Scale (GCS) (in some cases, when the size of epidural hematoma only slightly exceeds specified volume and patient’s stage is fully compensated without symptoms, conservative treatment with dynamic CT control in the neurosurgical hospital is acceptable — the opinion of the authors of this article).

Epidural hematoma characterized by the volume of less than 30 cm³ and thickness of less than 15 mm and associated with displacement of midline structures of less than 5 mm in patients with consciousness level of more than 8 points on the GCS and without focal neurological symptoms may be subject to conservative treatment (with careful neurologic monitoring in neurosurgical hospital).

Time schedule and methods of the surgery

Patients with acute epidural hematoma should undergo emergent surgery, when it is indicated.

There is no consensus on the choice of surgical methods, but it is believed that craniotomy provides more complete evacuation of hematoma.

Definition

Acute epidural hematoma is a focal extracerebral hemorrhage, hyperdense on CT, located intracranially between the dura mater (DM) and skull bone.

Incidence

The sources using CT data as the primary diagnostic method report the incidence of epidural hematoma within the range of 2 to 5%. Increased severity of TBI is associated with higher incidence epidural hematomas (up to 10%). The peak incidence of epidural hematomas is observed in TBI patients aged 20 to 40 years. Epidural hematomas are rare in elderly and pediatric patients.

Location

Epidural hematomas are most often located in the temporal and temporoparietal areas. The incidence of bilateral epidural hematomas is less than 5%.

Clinical presentation

At admission, the level of consciousness is reduced to coma in 50% patients with epidural hematoma. The remaining 50% of patients have a lucid interval. Anisocoria and/or depression of the photoreaction develops in 45% of patients, focal neurologic signs (hemiparesis, epileptic seizures, etc.) occur in 30%.

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Concomitant intracranial hemorrhage is observed in 30—50% of patients.

**Treatment methods**

No prospective randomized studies discussing the choice of surgical or conservative treatment were found in the scientific literature. There are also no studies reporting the conservative treatment of epidural hematomas larger than 30 cm³. Patients with hematoma thickness of more than 15 mm and displacement of midline structures of more than 5 mm are significantly more likely to develop clinical signs of dislocation and herniation. The positive results of conservative treatment of epidural hematomas were reported only in patients with reduced consciousness up to 10—15 points on the GCS, average hematoma volume of 26.8 cm³, displacement of midline structures of less than 10 mm, and hematoma thickness of not more than 12 mm.

**Time schedule of the surgery**

Time schedule of surgical intervention depends on clinical symptoms of dislocation and herniation. Duration of these symptoms of more than 30 minutes significantly worsens outcomes, and duration of more than 1 hour can be lethal.

**Outcomes**

In patients with epidural hematomas, postoperative mortality is 10 to 30%.

**Predictors of poor outcomes**

Age, depression of consciousness, anisocoria or bilateral mydriasis, intracranial hypertension, hematoma size of more than 30 cm³, and displacement of midline structures by more than 10 mm are unfavorable prognostic factors. Hematoma size of more than 50 cm³ is associated with increased postoperative mortality.

**Surgical treatment of acute subdural hematomas**

Patients with 10 mm-thick or thicker acute subdural hematoma or displacement of midline structures by more than 5 mm should undergo surgical removal of the hematoma, regardless of the consciousness level.

All comatose patients with acute subdural hematoma are subject to intracranial pressure monitor.

Surgery is also indicated to patients with subdural hematoma thickness of less than 10 mm and displacement of midline structures by less than 5 mm, when there is decrease in consciousness level since the injury by 2 points or more as assessed on GCS, asymmetry of the pupils or lack of photoreaction; increase in intracranial pressure by more than 20 mm Hg.

**Time schedule and methods of the surgery**

Patients with acute subdural hematoma should undergo emergency surgery, when it is indicated.

Removal of acute subdural hematoma is carried out by craniotomy with retained or removed bone flap and plastics repair of the DM.

**Definition**

Acute subdural hematoma is a focal extracerebral hemorrhage, hyperdense on CT, and located between the brain surface and the DM.

**Incidence**

The sources, using CT data as the primary diagnostic method, report the incidence of subdural hematomas within the range of 10 to 30%. Subdural hematomas are less common in patients with mild to moderate traumatic brain injury compared to those with severe injury. Peak incidence of subdural hematomas is observed in TBI patients aged 30 to 50 years. In most young patients with subdural hematoma, injuries are caused by road traffic accident (RTA), while in the elderly patients they are mostly caused by falling. In 70% of comatose patients with subdural hematomas, brain injury is caused by the accident.

**Clinical presentation**

Consciousness level is decreased to coma in 50—70% of patients with acute subdural hematomas and lucid interval is observed in 40% of patients. Symptoms of brain dislocation, such as anisocoria and/or depression of photoreaction, have been reported in 50% of patients. In 60% of patients, acute subdural hematomas occur in combination with other intracranial traumatic injuries, traumatic intracerebral hematoma and focal brain contusion being the most frequent of them (60% of all observations and 80% of comatose patients). In 25% of patients, traumatic subarachnoid hemorrhage is observed, and 15% have concomitant epidural hematomas.

**Treatment methods**

We found no prospective randomized studies discussing the choice of surgical or conservative treatment in the scientific literature. In 25% of conscious patients with acute subdural hematomas and displacement of midline structures by more than 5 mm, who have no brain dislocation symptoms, delay development of clinical presentation of dislocation syndrome is possible, and therefore surgical intervention is required. No advantages of decompressive craniotomy over osteoplastic one were found, when removing acute subdural hematomas.

**Time schedule of the surgery**

Postoperative mortality increases in cases when consciousness level was reduced to coma for more than 2 hours. In comatose patients, who underwent hematoma removal within 4 hours, postoperative mortality was
30%, while in cases of later removal it was 90%. In patients with anisocoria or bilateral mydriasis and duration of symptoms for more than 3 hours prior to the surgery, postoperative mortality was 60%.

Outcomes
In patients with subdural hematomas and brain dislocation symptoms, postoperative mortality is 40—60%. Postoperative mortality in comatose patients is 60—70%. In cases when hematoma thickness is less than 10 mm, postoperative mortality does not exceed 10%, while in cases when hematoma thickness is more than 30 mm, it is up to 90%.

Predictors of poor outcomes
Age over 60 years, reduced consciousness up to coma, anisocoria or bilateral mydriasis, intracranial hypertension of more than 20 mm Hg, and displacement of midline structures by more than 10 mm are predictors of poor outcome of surgical treatment of patients with acute subdural hematomas.

Surgical treatment of contusions/crush injuries of the brain and intracerebral hematomas
In cases of focal crush injuries of the brain, causing progressive worsening of neurological status, persistent intracranial hypertension refractory to conservative treatment or with mass effect signs on CT, surgery is required.

In comatose patients, surgical treatment is carried out in cases when the volume of the frontal lobe injuries exceeds 30 cm³, the volume of temporal lobe injuries exceeds 20 cm³, midline structures are displaced by 5 mm or more, or there are CT signs of cistern compression, and if the total volume of injury exceeds 50 cm³.

Time schedule and methods of the surgery
Patients with traumatic intracerebral hematomas and focal brain contusion should undergo emergency surgery, when it is indicated.

Conservative treatment of patients with traumatic intracerebral hematomas and focal brain contusions is possible, when there is no augmentation of neurological symptoms, increased intracranial pressure, compressed basal cisterns, and the treatment is carried out in neurosurgical department and includes clinical monitoring and CT over time.

Decompressive surgery
Decompressive operations, involving infratemporal decompression, temporal lobectomy at the side of the non-dominant hemisphere, and hemicraniectomy, can also be indicated in the case of the pronounced lateral dislocation and persistent intracranial hypertension in patients with clinical and CT signs of tentorial herniation.

Bifrontal decompressive craniotomy within the first 48 hours after injury is the method of choice for treatment of patients with diffuse cerebral edema and intracranial hypertension without mass effect that are refractory to conservative treatment.

Definition
Focal contusion/crush injury of the brain and intracerebral hematomas account for focal intracerebral hemorrhage, hyperdense at CT. Delayed intracerebral hemorrhage is a phenomenon of the development of intracerebral hemorrhage in brain parenchyma that was intact during the baseline CT or increase in the severity and volume of bleeding over time.

Literature review and basic principles [2, 12—15, 23, 27, 31—37, 43, 47, 55, 57, 59—65, 80—114].

Incidence
The sources using CT data as the primary diagnostic method report the incidence of intracerebral hemorrhage within the range of 10 to 30% of all TBI patients. The incidence is much higher in cases of severe injury compared to more mild injuries. Delayed hemorrhage in the brain parenchyma that is intact during the baseline CT occurs in 3—8% of patients with consciousness level of less than 13 points on the GCS. Increase in the volume and/or severity of intracerebral hemorrhage early (3 to 12 hours) after the injury was observed in more than 50% of patients. Delayed hemorrhage can occur within 48 hours after the injury. Delayed hemorrhage occurs in 70% of patients with any traumatic pathology detected during baseline CT. Delayed hemmorhages are most common after decompressive operations, and in the case of systemic disorders (hypo/hypercoagulation, hypertension, etc.).

Clinical presentation
90% of patients with intracerebral hemorrhage volume exceeding 50 cm³ develop consciousness disorders and signs of dislocation and brainstem herniation. In most patients with focal contusions/crush injuries of the brain and intracerebral hematomas, who also have dural hematomas, intracranial pressure exceeds 30 mm Hg.

Methods of treatment
In most patients with focal contusions/crush injuries of the brain and intracerebral hematomas, osteoplastic craniotomy followed by removal of focal contusion/crush injury of the brain and traumatic intracerebral hematoma is the method of choice. Removal of hemorrhage focus reduces the degree of midline structure displacement and intracranial pressure. Extensive decompressive craniotomy with plastic repair of DM and/or external drainage of cerebrospinal fluid is possible. Selection of surgical method depends on the type (focal contusion/crush injury of the brain or intracerebral hematoma), location (highly functional areas of the
brain), hemorrhage volume, severity of brain edema, and intracranial pressure level. Decompressive surgery (internal and external) significantly reduces intracranial pressure and is used in the cases when conservative therapy in ineffective. There are no proven advantages of decompressive craniotomy over conservative therapy in patients with brain contusions.

**Time schedule of the surgery**

Time schedule of surgical intervention is based on clinical symptoms of dislocation and herniation. Postoperative mortality is significantly higher in cases when intracranial pressure is above 30 mm Hg. Surgical outcomes are significantly better, when surgery was carried out before dislocation symptoms occurred (even short-term). Surgical outcomes are significantly better, when decompressive craniotomy was performed within the first 2 days after the injury.

**Outcomes**

In patients with intracerebral hemorrhage, mortality ranges 16 to 72% and is mainly due to the development of delayed hemorrhage.

**Prognostic factors for poor outcomes**

In patients with contusions/crush injuries of the brain and traumatic intracerebral hematomas, risk factors for poor outcome include: age over 60 years, consciousness level 8 points or less on the GCS, intracranial hypertension, photoreaction disorders, anisocoria, hemorrhage volume exceeding 30 cm³, arterial hypoxia and hypoxemia, and multiple intracranial hematomas. Type of contusion/crush injury of the brain, as well as its location, are not independent prognostic factors.

**Indications for the surgery on the posterior fossa [51, 115]**

In patients with the posterior fossa injuries, absolute indications for the surgery include epidural hematomas larger than 25 cm³, damage to the cerebellum larger than 20 cm³, occlusive hydrocephalus, and lateral dislocation of the fourth ventricle.

Conservative treatment of patients with injured posterior fossa structures can be carried out in cases, when epidural hematoma volume is less than 10 cm³, lateral injuries of the cerebellum are less than 10 cm³, and there is no displacement of the fourth ventricle and brainstem symptoms.

Expectant management of patients with injured posterior fossa structures is possible in cases, when epidural hematoma volume is 10 to 20 cm³, and volume of cerebellum injury is 10 to 20 cm³. Treatment strategy should be chosen with allowance for the consciousness level, ocular fundus state, and the results of acoustic stem evoked potentials. Such patients should be subjected to dynamic CT studies with allowance for the risk of delayed hematomas, rapid development of liquor pathway occlusion, and decompensation of the patient.

**Surgical treatment of depressed skull fractures**

In cases of depressed skull fracture deeper than bone thickness, surgery is required.

Patients with open depressed skull fractures can be treated conservatively, unless there are signs of DM damage, large intracranial hematoma, depression greater than 1 cm, involvement of air sinuses, cosmetic defect, wound infection, pneumocephalus, or heavily contaminated wounds.

Decision on the conservative treatment of closed depressed fracture is made individually in each case.

**Time schedule and methods of the surgery for depressed fractures**

Early surgery is advisable in order to reduce the risk of infection.

Elimination of depressions and wound debridement are essential elements of the operation.

If the wound is not infected, primary bone grafting is possible.

Therapeutic measures for open depressed fracture should include antibiotics.

**Incidence**

The sources using CT data as the primary diagnostic method report that the incidence of calvarial bone fractures is 6% of all TBI patients. The incidence of depressed fractures of the calvarial bones is 20—25% of all patients with calvarial bone fractures.

**Clinical presentation**

Various intracranial hematomas are observed in 40—70% of patients with calvarial bone fractures. The incidence of intracranial suppurative complications in patients with calvarial bone fractures ranges from 2 to 10%. The incidence of late posttraumatic epileptic seizures is up to 15%. The highest risk of post-traumatic epilepsy is observed in patients with DM injury caused by fragments of depressed fracture. In cases of depressed fractures deeper than bone thickness, probability of DM injury is about 90%.

**Treatment methods**

We found no prospective randomized studies discussing the choice of surgical or conservative treatment. Not all depressed fractures are subject to surgical treatment. In most cases, primary surgical treatment of the wound (if any), and elimination of depressions using the available bone fragments is the method of choice in the treatment of depressed fractures. The need for surgical treatment is primarily determined
by the risk of epilepsy and suppurrative complications. Furthermore, deformation plays an important role, when the fracture is located at a cosmetically important area. When there are open and particularly penetrating injuries at the area of depressed fracture, surgery reduces the risk of septic complications up to 5%. There are no advantages of resection trepanation over osteoplastic one. Primary bone grafting using autogenous bone graft (bone fragments) does not increases the risk of septic complications. In the case of closed TBI with the fragments of depressed fracture located out of paranasal and venous sinuses, the risk of infectious complications and post-traumatic epilepsy associated with conservative therapy does not exceed the risk associated with surgical treatment.

**Time schedule of the surgery**

Surgical treatment of depressed fractures in combination with open TBI performed after 36 hours is associated with increased number of septic complications up to 37%. In patients with closed TBI, the risk of septic complications is minimal and does not depend on the time of the operation.

**Outcomes and predictors of poor outcomes**

In patients with depressed fractures, outcomes are mainly determined by the presence of concomitant intracranial pathology, i.e. intracranial hemorrhages and intracranial hypertension, as well as the risk of intracranial suppurrative complications caused by open TBI and wound liquorrea. Mortality of patients with TBI and depressed fractures ranges from 1 to 20%.

Management of patients with intraventricular hemorrhages, skull base fractures, basal liquorrea, and craniofacial trauma will be discussed in part 4 of these Guidelines.

**Authors declare no conflict of interest.**

**REFERENCES**


**New Simulation Technologies in Neurosurgery**

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The article presents a literature review on the current state of simulation technologies in neurosurgery, a brief description of the basic terminology and the classification of simulation models, and examples of simulation models and skills simulators used in neurosurgery. Basic models for the development of physical skills, the spectrum of available computer virtual simulators, and their main characteristics are described.

It would be instructive to include microneurosurgical training and a cadaver course of neurosurgical approaches in neurosurgery training programs and to extend the use of three-dimensional imaging. Technologies for producing three-dimensional anatomical models and patient-specific computer simulators as well as improvement of tactile feedback systems and display quality of virtual models are promising areas. Continued professional education necessitates further research for assessing the validity and practical use of simulators and physical models.

**Keywords:** simulation, neurosurgery, models, education, training, microneurosurgery.

Simulation training is a relatively new and progressively developing area of medicine over the past few years [1, 2]. The significance of simulation technologies for neurosurgery as the scientific knowledge and practical discipline is undeniable [3]. Nevertheless, it should be noted the real issues of neurosurgery, where the introduction of simulation technology is particularly useful and has a significant potential for further development.

By the order of Ministry of Health of the Russian Federation dated December 5, 2011 No. 1475n, the extent of residency simulation training course is 136 hours. According to the Russian society of simulation training in medicine (ROSO-MED), in 2014, there are about 50 simulation centers in Russia, and until 2017 it is planned to set up at least 80 centers. By keywords “simulation” and “neurosurgery” in the databases Pubmed and Elibrary, there are more than 1,500 articles, and the number of publications on this subject per year are constantly increasing.

The purpose of this review is to study current contemporary state of simulation technologies in neurosurgery.

**Terminology and classification**

In this context, simulation is an imitation, modeling and realistic reproduction of process.

Proposed classification of simulation models for neurosurgical operations (skill simulators):

1. Physical (material) [1].
   1.1. Tissue:
       a) live models (laboratory animals);
       b) tissue (cadaver dissection, chicken wing, placenta).

1.2. Artificial (synthetic prostheses, phantoms, dummies).

2. Virtual (virtual simulators).
   2.1. Models of augmented reality.
   2.2. Completely virtual models.

The value of physical models is limited for a simulation of the entire medical intervention, but they may be useful for a simulation of separate phases of intervention [4]. There are a part-task simulation and procedural simulation.

Simulation biological models supposed to use a wide variety of material. For example, laboratory rats and mice were used for the practice of microneurosurgical skills for a long time [5]. The practice of laparoscopic and thoracoscopic, endovasal and cranial surgery has carried out in vivo on pigs [6]. Cadaver dissection is a type of simulation, which is actively used in neurosurgical education since the Renaissance [7].

Computer simulators are based on the creation of three-dimensional or two-dimensional virtual model simulating the morphology, disease, physiological condition, diagnostic procedures or surgical intervention. One of the terms of virtual simulation is haptics. Haptics (from the Greek hapto is to touch, to grab) is a property of tactile feedback in the simulator. Augmented reality is created by real physical objects displayed on screen or in the eyepieces when the computer-simulated image projects on them [8, 9].

It is important to develop useful and practical simulation models, which is necessary to prove the validity [10]. Valid [from the French valide is significant, current] is a current, efficient, meeting the requirements [11]. Validity is an efficient utilization of simulator or
simulation techniques according to the principles of evidence-based medicine [12].

Global approach to simulation training in neurosurgery

Based on prior experience of training course for pilots [13], the US Society of Neurological Surgeons developed a formal annual training course known as “Basic training” for the first-year residents. [14] The course includes skill training for different interventions:

1) puncture of ventriculoperitoneal shunt system and valve programming;
2) installation of lumbar drainage;
3) installation of intracranial pressure sensor;
4) external ventricular drainage;
5) catheterization of central veins and arteries;
6) emergency action training (six model-based simulations):
   a) use of the surgical microscope and instruments;
   b) types of patient position on the operating table;
   c) stages of craniotomy to remove a subdural hematoma after brain injury: use of drill, creation of bone flap, dissection and closure of dura mater, fixation of bone flap and skin suturing.

It may be useful to hold such courses on a scale of federal districts under the aegis of Association of Neurological Surgeons in the large simulation centers.

Further, the review describes basic simulation models in various neurosurgical areas.

Debriefing and simulation of neurosurgical patients

In neurosurgery as well as in other high-risk areas, the success of intervention is often associated with the non-technical aspects such as optimal teamwork, leadership, situational awareness, decision-making and interpersonal communications [15]. It is shown that the set of adverse events are caused by human factors, and many errors can be prevented by effective teamwork [16]. For example, S. Harnof et al. [16] presented the results of simulation training of communication skills for neurosurgeons through scenarios with actors. Scenarios include obtaining informed consent for intervention, discharge talking, informing about complications, informing the parents about the child’s brain tumor and brain death. The training of such scenarios at the national level is likely to become mandatory part of the residency neurosurgical program in Israel.

Cadaver dissection laboratory in neurosurgery

According to a survey conducted by V. Kshettry [17], 95.4% of managers in the US neurosurgical programs are confident that laboratory dissection should be a mandatory part of the educational program in neurosurgery; while none of the respondents did not consider that a virtual simulation is capable of great benefit compared to laboratory dissection. Currently, the legal and technical possibility of cadaver providing the sectional halls of Russian medical universities is a topical issue. There is a lack of high quality prepared injected specimens which can be used for training and development of different cranial approaches, for scientific purposes [18]. On the other hand, physical and virtual 3D-models may replace them in some way.

Craniotomy simulation

A common model for training of high-speed drill manipulation is a cow scapula. This material is the most available, cheapest and safest. Different skull models are used for training of various neurosurgical skills for bone flap fixation, cranioplasty and neuronavigation (Sawbones, Kezlex etc.) [19]. For the practice of wound suturing after craniotomy, it is used the skull model with artificial skin similar in structure to the soft tissues of the skull. For example, a “basic training” for residents includes the simulation of clinical case: after receiving the information about sudden deterioration of “Patient” condition in the emergency room because of the increasing of traumatic intracranial hematoma, decompressive craniotomy is performed on dummy in the simulated operating room.

Neuroendoscopy

Among the first R. Sierra et al. [20] reported a simulation ventricular system phantom with the possibility of a virtual patient-specific preoperative training and “intraoperative” navigation for the study of ventriculoscopic interventions.

The development of simulation models of endoscopic transnasal surgery is also highly relevant. Currently, it is known the virtual computer models (NeuroTouch), physical models based on polymeric embalming [18] and phantoms for training of transnasal transtonoidal and ventricular endoneurosurgical skills. For example, the simulator S.I.M.O.N.T. allows studying surgical anatomy of the ventricular system, training skills of rhinosinusal endoscopy and transphenoidal approach [21]. At Stanford University, it is developed the virtual simulations for patient-specific endoscopic anatomy of paranasal sinuses and temporal bone surgery [22].

Microanastomosis creation

A variety of models has been proposed for training of microanastomosis creation skills under the table [23] or neurosurgical microscope: gauze [24], silicone tubes [25], rat vessels [5], placental vessels [26], and cooled chicken or turkey wing [27]. More complex model is one for training of anastomosis creation in the deep operative field [28, 29].

Arachnoid dissection and aneurysm clipping

Initial microneurosurgery skills should be obtained using a laboratory training [30, 31]. For example, T. Hicdonnez et al. [32] described a microneurosurgical model of fresh cow brain for training of manipulation with microinstruments and microdissection. To develop arachnoid dissection skills, an effective training is the
Dura mater closure
The model includes a thin sheet of artificial dura mater, stretched over a soft silicone dummy brain localized in the skull model for training of guy suture application and dura under closure for mechanical restraint of the bone window [34]. It is very useful for training of spinal dura mater closure skills [35].

Shunt device puncture
The simulation includes puncture of reservoir valve, which is connected to a saline infusion line. Then, it is performed a puncture of the same valve, but covered with artificial leaether, which allows to palpating and puncture the reservoir to obtain the tactile feedback similar to a real one.

Endovascular neurosurgery
For the simulation of endovascular interventions, there are physical dummies and silicone models [36] of large laboratory animals (pigs) with formed aneurysm or arteriovenous malformation [37]. In recent years, the virtual computer models to simulate endovascular interventions become more popular. Endovascular simulator includes training modules for a wide variety of the coronary, peripheral blood vessels and aorta interventions [38]. Only a few trainers include cerebral modules. An important advantage of these simulators is the possibility to simulate arteriotomy or its main stages the presence of tactile feedback, as well as the possibility to change the neurological and physiological hemodynamic parameters, and to measure and evaluate skills. The cost of this device is about 2-11 million rubles depending on the manufacture and program modules. The cost of annual service is up to 300 thousand rubles. Additional costs include insurance and personnel training. In neurosurgical practice, endovascular simulators allow training the skills of aneurysm coiling, carotid and cerebral arteries stenting, balloon angioplasty, selective drug administration and thrombectomy [39].

Lumbar puncture
The physical dummies and virtual simulators with tactile feedback have been developed for lumbar puncture training [40].

Spinal neurosurgery
Various physical and virtual models have been developed to practice interventions. T. Halis et al. [41] presented the model of simulator for training of disc hernia removal at the cervical level based on augmented reality. Intervention planning and manual skills training are implemented in the three-dimensional physical models made of material similar in structure to the bone tissue (Sawbones, USA). These dummies are validated for practice of foraminotomy and laminotomy at the cervical level [42], and training of the optimal trajectory for pedicle screw installation [43]. The training of pedicle fixation and vertebroplasty is also available in the virtual simulators Sensimim [44]. The dummies for lumbar discectomy surgery, which allow the resection of bone, evaluating nerve root tension, dural sac compression and bleeding have been developed [45]. New simulator 3S (Surgical Spine Simulator) for preoperative planning of scoliosis correction allows evaluating the intended result and fixing screw stress [46]. Box simulator with a fixed spine of cadaver or laboratory animal allow training the skills of minimally invasive interventions [47].

Computer simulators
Neuro Touch is one of the first virtual simulators. Currently, it allows training the basic skills of aspirator tip, ultrasonic aspirator-destroyor and bipolar forceps manipulation, and evaluating the fundamental principles of hemostasis, endonasal navigation and ventriculostomy. Furthermore, the modules are available for the simulation of menigioma and glioma resection. In case of contact with rigid or flexible structures, their resistance is simulated by the tactile feedback system, which is similar to other virtual simulators.

Another computer virtual feedback 3D-simulator ImmersiveTouch Sensimim (Immersive-touch, USA) allows training the skills of craniotomy, ventricular catheterization and rhizotomy. The simulator is available modules of lumbar puncture, pedicle screw installation, vertebroplasty and other simulation operations. [44] Dextroscope (Bracco AMT Inc., USA) is a workstation capable of three-dimensional reconstruction of digital medical images and neurosurgery simulation including tumor removal, aneurysm clipping [48] and virtual temporal bone dissection [8]. Screen image reflects in the mirror and is perceived as three-dimensional through the shutter glasses synchronized with the screen. Unfortunately, the limitation of this system is the lack of tactile feedback. The company Bracco has developed devices and software of a virtual reality, a patient-specific volumetric images for editing and presentation using Dextrobeam [49]. The next development is the creation of augmented reality system for surgery Dex-ray. The device consists of a space-monitoring probe with integrated tiny camera. The camera receives a tip probe image of the operative field. The camera’s video stream is augmented with coregistered, multimodality 3D graphics and landmarks obtained during preoperative planning with workstation Dextroscope, and provides the “see-through” vision [9, 50].
The newly developed simulator SuRgical Planner (Surgical Theater, USA) allows obtaining virtual three-dimensional reconstructions to simulate cerebral aneurysm clipping. A feature of this simulator is the possibility of distance education and collaborative remote work using just one device [51].

**Patient-specific model creation**

The development of patient-specific three-dimensional reconstructions for education and preoperative training is the future of virtual surgical simulators [52], however, their implementation will require considerable time. It is now implemented projects on the integration of patient data, such as aneurysm clipping simulation on simulators Destroscope and Surgical Rehearsal Platform, and tumor resection on simulator NeuroTouch.

The modern software provides an automatic and accurate three-dimensional reconstruction of normal and pathologic anatomy of the patient using instrumental examination data (CT, MRI, DSA) [53]. Digital three-dimensional images may be edited and used for planning and rehearsals of various surgical interventions. [54] Rapid prototyping techniques (3D-printers) can print three-dimensional anatomical models for planning of approach and physical simulation of intervention based on the anatomy of skull bones, cerebral vessels, membranes and tissues [55]. Another useful and promising technique is to create some three-dimensional photographic and video atlases of microneurosurgical approaches [56].

**Multitouch feedback in computer simulators**

All virtual neurosurgical simulators consist of three main components: a manipulator with tactile feedback (known as "sensory sculptor", "haptic stylus"); system for displaying a three-dimensional image; a powerful computer with specific software. The accuracy of manipulator positioning, e.g. Geomagic Touch, reaches 0.023 mm and a maximum load of 7.9 N.

It is planned to produce cheaper and improved virtual simulators and robots based on the haptic technology. For example, the Tokyo Institute of Technology conducted a study of surgical robot IBIS using mentioned above haptic stylus [57], which can compete with the robot da Vinci on quality, tactile feedback and cost.

**Areas for further research and development of simulation techniques in neurosurgery**

Simulation techniques have a great potential for the neurosurgery development due to the fact that they provide an opportunity for a better understanding of spatial relationships on three-dimensional images, which is important not only for training, but also for planning of the intervention components. Augmented reality technology provides "see-through" vision, expanding the opportunities of intraoperative navigation [58].

High complexity and diversity of neurosurgery techniques make difficulties in the development of simulation models, but in the past few years it has been achieved a significant progress in this area. In different parts of the world, neurosurgeons in collaboration with engineers developed different simulation models that contribute to training of the beginners and practicing neurosurgeons from basic skills of ventriculopunction and craniotomy to more complex skills of tumor dissection, skull base surgery, endoneurosurgery and vascular microneurosurgery. Students and residents have the opportunity to develop new skills on the simplest models. More relevant physical and virtual models contribute to the professional development, assimilation and improvement of surgical techniques even in experienced neurosurgeons [59].

Comparing the development of simulation technology in other areas of medicine, it is supposed that centralization and standardization of the neurosurgery educational programs is a promising direction. It may be useful to include microneurosurgical training and cadaver course of neurosurgical approaches in the specialty training and development program "Neurosurgery", as well as to extend the use of three-dimensional (microscopic and endoscopic) imaging in the practice and educational process. In methodological aspects, it is relevant to develop the standards of competence-based approach to expert and valid qualimetric test evaluation.

Considering the high cost of virtual computer models, it is especially important to develop a cheaper physical model for training of specific neurosurgical skills of microdissection, Anastomosis technique, intraventricular and transsphenoidal endoscopic surgery. Promising directions are the scientific and technical development of import-substituting production of patient-specific physical models and virtual simulators, improvement of tactile feedback systems and increasing the quality of virtual model reproduction. In the context of evidence-based medicine, further studies are required to evaluate the validity and practical use of simulators and physical models.

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Transcranial focused ultrasound is a modern medical technique, which provides non-invasive impact on the brain. Current development stage of this technique is no longer than 20 years and many possible applications of this technique are still at pre-clinical stage. The greatest progress has been made in the field of functional neurosurgery. Focused ultrasound enables non-invasive MRI-guided formation of small destruction foci in the relevant targets, providing therapeutic neuromodulating effects in patients with Parkinson’s disease, essential tremor, pain syndromes, obsessive-compulsive disorders, and other diseases. So far, this treatment was carried out in more than 300 patients. Several cases of ultrasound thermal destruction of intracranial neoplasms were published. There are attempts to perform third ventriculostomy using ultrasound in animals. A separate area focuses on the enhancement of the permeability of the blood-brain barrier to various substances driven by focused ultrasound. The possibilities of enhancing the permeability to chemotherapeutic agents, immune drugs, and other substances are being investigated in laboratories. A large number of studies focus on treatment of Alzheimer’s disease. Clinical trials aimed at enhancing the permeability of the blood-brain barrier to chemotherapeutic agents have been initiated. Reversible neuromodulating, stimulating, and inhibiting effect of focused ultrasound on the nervous system structures is another non-destructive effect, which is currently being actively investigated in animals. Furthermore, laboratory studies demonstrated the ability of focused ultrasound to destroy blood clots and thrombi.

Transcranial focused ultrasound provides numerous unique possibilities for scientific and practical medicine. Large-scale research is required prior to the widespread clinical implementation. Nevertheless, we can already state that implementation of this technique will significantly enhance diagnostic and therapeutic potential of neurosurgery and neurology.

Keywords: ultrasound, focused ultrasound, neurosurgery, functional neurosurgery, blood-brain barrier.

The use of minimally invasive technologies is one of the main trends in the development of surgical disciplines. In neurosurgery, these technologies reduce the risk of neurological complications and improve the cosmetic outcome of an operation. Non-invasive impact methods are the next stage of the development of surgery, which could replace direct intervention and eliminate the associated risks of bleeding, infection, and tissue injury.

Focused ultrasound, a new method in neurosurgery, has been intensely discussed in the papers over the past few years. Non-invasive destruction of intracranial targets is one of the many possible applications of this method. Many other potential therapeutic and diagnostic applications of this technique have also been proposed.

The purpose of this work is to provide an overview of therapeutic and diagnostic potential of focused ultrasound.

The history of the development of the method of focused ultrasound

Early experiments with high-intensity focused ultrasound irradiation to produce non-invasively local cerebral destructive lesions were initiated by J. Lynn et al. [1] in the early 40s and continued by brothers W. Fry.
Ultra sound therapy was delivered through a craniotomy window without incision of cerebral meninges. In the 50s ultrasound destruction was produced in patients with Parkinson’s disease and psychiatric disorders [3—5]. Despite the progress, utilization of ultrasound was limited by several factors, such as requirement for craniotomy and failure of precise navigation.

These technical problems were resolved only in the late 90s. The problem of delivering ultrasound therapy through the intact skull bones, which attenuate significantly ultrasound and become heated, was resolved with the help of ultrasound phased array technology [6—8]. Each array has a transducer which adjusts phase shift so that the waves from different array elements are focused simultaneously on the target. A hemisphere-shaped transducer disperses evenly the ultrasound over the skull [6]. MRI and MR thermometry enabled a non-invasive real-time monitoring of tissue temperature during ultrasound thermal destruction [9, 10].

**Biophysics and mechanism of action of focused ultrasound**

The modern principle of FUS technology is based on the use of one or more sources that focus ultrasound waves with certain parameters on the targeted focus to cause a desired biological effect (for example, destruction, changes of vascular permeability) under ultrasound or MR-guided control.

FUS technology uses waves with a frequency of less than 1 MHz (the frequency of diagnostic ultrasound is 1—15 MHz), which reduces heating of the skull bone [6, 11]. At ultrasound exposure of high intensity thermal destruction of tissue is achieved (> 100 W/cm²), while at low intensity levels beneficial non-thermal effects may be produced [11, 12]. Therapeutic ultrasound energy is usually delivered as continuous waves (used for thermal destruction) or short pulses (for neuromodulating effects).

The biophysical effects of FUS are described in a number of papers [13, 14]. Ultrasound is an acoustic mechanical wave that propagates through an elastic medium. The area of high pressure is followed by a low pressure area, and every particle of an elastic medium vibrates.

Friction of the particles when they vibrate causes mechanical energy to be transformed into thermal energy. Coagulative necrosis occurs at intense or prolonged exposure (at 56°C for 1 s and at 42°C for 240 s) [15].

Ultrasound also causes cavitation. At stable cavitation vibration of existing in the tissue or injected microbubbles occurs, leading to increased vascular permeability. Transient cavitation of microbubbles occurs with volume expansion followed by collapse and rapture of microbubbles. During the collapse, extremely high amount of energy is generated leading mechanical destruction of a tissue. Potential use of regulated cavitation-induced tissue damage is under study, but so far, cavitation cannot be controlled well and is mostly regarded as a side effect of thermal ablation.

The parameters of the ultrasound wave determine physical effects which, depending on the location and the application conditions, may have different biological effects.

**Focused ultrasound equipment**

Specialized manufacturers develop a wide range of ultrasound sources. Standard FUS sources, which are not specifically designed for interventions on the brain, are used in most of the experimental works.

All of the modern clinical research and also a major part of the experimental works are performed using the ExAblate Neuro device (InSightec, Haifa, Israel). In clinical practice, this system is used for non-invasive ultrasound thermal ablation of brain targets. Currently, this device was approved for clinical practice in Europe (CEMark) for thalamotomy in patients with essential tremor and neuropathic pain. Under laboratory conditions, the feasibility of using this device has also been demonstrated to perform cavitation-induced tissue destruction and also for local BBB permeability enhancement [16, 17].

**Construction of the ExAblate Neuro 4000 device**

The current model of the ExAblate Neuro 4000 (InSightec, Haifa, Israel) system contains a helmet with a diameter of 30 cm and uses a 1024-element phased-array transducer operating at 650 kHz (Fig. 1). The phased-array transducer enables targeted delivery of ultrasound. A flexible silicone membrane seals the space between the patient’s head and the helmet. The circulating water provides acoustic coupling and head cooling. The helmet with array elements is attached to a 3T or a 1.5T MRI scanner (General Electric).

**Thermal destruction procedure**

Thermal destruction using the ExAblate 4000 device is a standard procedure [18—20]. The patient’s head is...
fully shaved as hair may promote formation of air microbubbles creating a risk of burns. A CRW stereotactic frame (Radionics) is fixed to the patient’s head. The patient is positioned on a special table with his head fixed in a helmet containing phased-array transducers. The table, on which the patient lies, slides into the tunnel. Preliminary MRI and CT scans with high resolution are loaded into the application for procedure planning. MRI is performed in the fixation system. The planning system identifies the target and the system is started. MRI provides real time monitoring to identify the location of the target and to monitor the temperature [21].

The treatment procedure involves applying a series of short (10—30 s) bursts of ultrasound energy with gradual increasing the power with each next switching on the transducer. Periods lasting for a few minutes between the switches on of a transducer provide cooling of the skin and skull and the patient’s condition is assessed for appearance of the clinical effect or complications.

At the first stage, the temperature that does not cause destruction is applied, that is 40—45°C [18, 19]. This stage is necessary to confirm the temperature focus localization. Further increase in the power and temperature may lead to unstable clinical effect and/or complications (paresthesias, speech disturbances, etc.). For example, patients showed improvement in tremor and pain syndrome as early as at 50°C [19, 20, 22]. When a satisfactory reversible effect is achieved the power is increased to achieve destructive temperatures of 55—63°C [18, 19].

Completion of destruction in the focus is judged from several parameters: achieved sufficient temperature, clinical effect, the appearance of complications, and MRI data. After completion of the procedure the patient is removed from the apparatus and the stereotactic frame is removed.

In treatment of tumors, destruction in several foci can be performed in order to destroy the whole tumor.

**Accuracy of the procedure**

Comparison of the accuracy of various stereotactic procedures in functional neurosurgery is presented in Table 1. Ultrasound destruction using the ExAblate 4000 system is characterized by high targeting accuracy that is at least not inferior to that in conventional stereotactic procedures [23—25]. The targeting accuracy of ultrasound destruction is thought to be higher than the accuracy of the invasive techniques that cause a slight displacement of the brain structures [23, 26]. In some situations, the technical parameters (for example, vertical MR thermometry data alignment accuracy) can lower the accuracy of the procedure [19]. These situations necessitate development and improvement of intervention protocols, ascquisition and use of MRI data [20].

**Limitations of the ExAblate Neuro 4000 device**

It is worth noting that currently the ExAblate Neuro 4000 device and technology of FUS exposure on brain targets have several limitations.

The possible impact zone in the recent model of the device is limited to an area within about 3.5 cm from the intercommissural line. Exposure on the target beyond of this zone results in excessive heat to the bone tissue near the focus and near the calvarium. The release of a new device model with the impact zone of about 6.5 cm from the intercommissural line has been announced.

Failure to achieve the necessary temperature for thermal destruction is a problem in some situations. In the work by W. Chang et al. [18] three patients of eleven could not complete the treatment with vim-thalamotomy because of insufficient temperature. H. Jung et al. [27] did not achieve results in 4 of 17 patients with ultrasound vim-thalamotomy and capsulotomy. It is assumed that the limitations may be associated with a large volume of the skull on the intercommissural line, the ratio of the thickness of the cancellous to compact bone of the skull, the shape of the skull and other factors. One way to address this problem is injection of microbubbles into the bloodstream (ultrasound contrast agent) that may potentiate thermal destruction [14]. A computational model to simulate focused ultrasound neurosurgery interventions that can predict parameters of thermal destruction before fixation of the stereotactic frame is developed [28].

The current model of the device differs by that it is designed for functional neurosurgery. This defines a small area of exposure thus complicating significantly destruction of tumors with significant sizes. The new model of the device has been announced to have the exposure zone extended up to several centimeters.

**Destructive neuromodulation**

Currently, ultrasound thermal destruction is primarily used in functional neurosurgery for Parkinson’s disease, essential tremor, obsessive compulsive disorder, depression, neuropathic pain, and other diseases [18—20, 27]. Ultrasound thermal destruction was approved for clinical use in several countries. So far, a total of more than 300 patients with functional disorders have been treated worldwide with this technology.

D. Jeanmonod et al. [20] presented the first major study on the use of FUS in functional neurosurgery. The authors evaluated outcomes of ultrasound thalamotomy in 9 patients suffering from neuropathic pain. Mean improvement score according to the visual analog pain scale decreased from preoperative values of 59.5/100 to 34.3/100 (42.3%) at 3 months and up to 35.3/100 (40.7%) at 1 year. Adverse effects during the procedure were observed: vestibular disorders, sometimes with vegetative symptoms (8 patients), paresthesia (4), and dysesthesia/pain (9). One patient developed dysarthria and dysmetria at the end of the procedure after completion of
improved from 20.4 to 5.2 (rating scale for tremor to calculate scores for tremor) of tremor suppression was measured using the clinical improvement. Scores for hand tremor (the effectiveness 12 months after treatment, all patients showed tremor. Thermal ablation occurred in all 15 patients. At unilateral vim-thalamotomy in 15 patients with essential treatment protocol.

or excessive sonication temperature rise (over 60°C) symptoms almost completely relieved. The authors changes regressed according to MRI data and the ischemia. At follow-up these destruction. MRI in the target area revealed a bleed in the target (8—10 mm) and ischemia. At follow-up these changes regressed according to MRI data and the symptoms almost completely relieved. The authors suggested that the complication was caused by cavitation or excessive sonication temperature rise (over 60°C) followed by the introduction of safety measures to the treatment protocol.

W. Elias et al. [19] reported outcomes of ultrasound unilateral vim-thalamotomy in 15 patients with essential tremor. Thermal ablation occurred in all 15 patients. At 12 months after treatment, all patients showed improvement. Scores for hand tremor (the effectiveness of tremor suppression was measured using the clinical rating scale for tremor to calculate scores for tremor) improved from 20.4 to 5.2 (p=0.001). Total tremor scores assessed from the clinical rating scale for tremor improved from 54.9 to 24.3 points (p=0.001). Quality-of-life scores improved from 37 to 11% (p=0.001). Adverse effects of the procedure included transient sensory, cerebellar, motor and speech abnormalities (during the procedure or after), with permanent paresthesia in four patients (tongue, lips, and fingers). Some patients experienced head pain, nausea, vomiting, “flushed” or “warm” sensation, “falling,” or “spinning” sensation, and light-headedness during the procedure. Syncope was reported for one patient.

In the same group of patients the dynamics of MR characteristics of the foci after ultrasound vim-thalamotomy was studied, and the relationship of these parameters with the clinical effect [29]. On T2-weighted MRI in the first day three concentric zones were identified in the foci: a hypointense zone I at the center, an intermediate strongly hyperintense zone II, and a slightly hyperintense zone III at the periphery. A cavity developed in the location of zones I and II at 1—7 days. This cavity collapsed by 1—3 months. Zone 3 was significantly reduced its size in a month and then resolved after 3 months. Postcontrast enhancement was seen in 6 patients at 24 hours. Enhancement appeared at 1 week in 6 patients, was present in 15 patients at 1 month and in 3 patients at 3 months. No intracerebral hemorrhage occurred, but blood degradation products were seen within zones I and II. Zones I and II likely represent areas of coagulative necrosis and cytotoxic edema, zone 3 — vasogenic edema [29—31].

Tremor control was optimal at 1 week when the lesion size and the perilesional edema were maximal, and it was less at 1 or 3 months when the perilesional edema resolved and the total lesion size was smaller [29]. The clinical effect remained when the cavity collapsed.

H. Jung et al. [27] published different MRI patterns after vim-thalamotomy (11 patients with essential tremor) and capsulotomy (6 patients with obsessive-compulsive disorder). In vim-thalamotomy, lesions were visible immediately after treatment and markedly reduced in size as time passed. Lesion size was merely visible immediately after sonication in capsulotomy, peaked at 1 week after treatment, after which lesion size gradually decreased and exceeded the initial lesion size at the end of follow-up period. The authors suggest that the differences likely relate to the type of the target: the ventral intermediate nucleus (vim) contains more nerve cell bodies and the internal capsule is a location where a large number of conductive fibers travel.

A. Magara et al. [32] reported treatment outcomes of 13 patients with Parkinson’s disease using unilateral ultrasound pallidothalamic tractotomy. The first four patients (group one) received a single application of the peak energy on the target and the procedure was terminated. That produced thermocoagulation volume of about 83 mm³ at 2 days on T2-weighted images. At 3 months, the mean relief according to the Unified Parkinson Disease Scale was 7.6%. For the next nine patients (group two), the peak energy application was repeated 4—5 times. The lesion volume was 172 mm³ on T2-weighted images at 2 days (Fig. 2) and the mean relief according to the Unified Parkinson Disease Scale was 60.9% in this group. No patients demonstrated any complications in the study.

In 2014, J. Chang et al. [33] and W. Elias et al. [34] presented the first results of ultrasound pallidotomy and subtalamotomy for Parkinson’s disease.

H. Jung et al. [35] published a work on the use of focused ultrasound for obsessive-compulsive disorders. In 4 patients, bilateral thermal capsulotomy to ablate the anterior limb of the internal capsule was performed. Patients underwent evaluations over the 6-month follow-up period. Outcomes were measured with the Yale-Brown Obsessive-Compulsive Scale, which showed a mean improvement of 33%. Sustained improvements in depression (a mean reduction of 61.1% according to the Hamilton Rating Scale for Depression) and anxiety

Table 1. Comparison of accuracy of different stereotactic functional procedures

<table>
<thead>
<tr>
<th>Paper</th>
<th>Method</th>
<th>Displacement</th>
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<tbody>
<tr>
<td>D. Moser et al., 2013 [26]</td>
<td>FUS</td>
<td>0.66 (SD 0.37)</td>
</tr>
<tr>
<td>W. Elias et al., 2013 [19]</td>
<td>FUS</td>
<td>2.2±2.4</td>
</tr>
<tr>
<td>N. Hamid et al., 2005 [24]</td>
<td>DBS</td>
<td>2.9</td>
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<tr>
<td>G. Bougeois et al., 1999 [23]</td>
<td>RFA</td>
<td>1.9</td>
</tr>
<tr>
<td>N. Massager et al., 2007 [25]</td>
<td>RS</td>
<td>0.33 (SD 0.29)</td>
</tr>
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(a mean reduction of 69.4% according to the Hamilton Rating Scale for Anxiety) were shown. Two of the four patients met the criteria for a full response (a greater than 35% improvement in the Yale-Brown Obsessive-Compulsive Scale). No demonstrable persistent complications occurred in these patients.

The published studies demonstrate the efficacy and safety of the procedure for functional disorders. Volume, localization, and MR characteristics of destructive lesions produced with ultrasound are consistent with those after radiofrequency thermal ablation [22, 36, 37]. The effectiveness of ultrasound tissue destruction appears comparable with effectiveness of radiofrequency thermal ablation and also stimulation of deep structures [18, 19, 22, 32, 35, 38-44]. The effectiveness of ultrasound tissue destruction appears comparable with effectiveness of radiofrequency thermal ablation and also stimulation of deep structures [18, 19, 22, 32, 35, 38-44]. Focused ultrasound of all destructive techniques seems the most appropriate, as this procedure versus direct stereotactic radiofrequency ablation, poses no risk of intracerebral hemorrhage, infection, and others and compared to radiosurgical treatment FUS provides the opportunity of physiological verification, predictable results and rapid appearance of the effect [19, 45—47].

Destruction of intracranial neoplasms

The feasibility of focused ultrasound utilization for non-invasive destruction of intracranial neoplasms is of great interest.

Two first non-invasive thermal ablation cases of brain neoplasms, glioblastoma and metastasis, using the ExAblate Neuro 4000 system were presented at 4th international symposium of current and future applications of focused ultrasound [48, 49]. In both cases, thermal ablation was successful. One of these cases is described in the publication by D. Coluccia et al. [50]. Both studies demonstrated a partial contrast enhancement of tumor destructive lesions on MRI after ablation (Fig. 3). Moreover, the procedure did not provoke neurological deficit in the patients despite deep tumor locations.

These cases of ultrasound destruction of brain tumors did not result in total destruction of the tumor and did not improve the condition of patients. Nevertheless, they proved, for the first time, the feasibility of using MRI-guided focused ultrasound for safe non-invasive ablation of brain tumors.

Destructive interference to normalize CSF circulation

One more potential application of FUS is internal shunting for some types of hydrocephalus instead of a shunt placement. S. Monteith et al. [51] in a review paper mentioned his experience of creation of a lesion in transparent septum and the floor of the third ventricle in cadaveric studies.

R. Alkins et al. [17] performed third ventriculostomy on pigs using MRI-guided focused ultrasound. They used ExAblate 4000 system with changed frequency settings to initiate inertial cavitation rather than heating. Different parameters of ablation were used. At 230 kHz, ventriculostomy was successful for tissue fractionation in the floor of the third ventricle and intraventricular membranes. MRI and morphological examination confirmed destruction.

Local enhancement of the blood-brain barrier permeability

Local and reversible blood-brain barrier disruption can be achieved by varying parameters of FUS [52]. Stable cavitation (rather than collapsing cavitation) is thought to be the basic mechanism for enhancement of BBB permeability [16, 53].
N. Sheikov et al. [54] investigated FUS-induced changes in rabbit brain capillary morphology by microscopy and immunohistochemical examination. The authors identified several mechanisms of capillary walls permeability enhancement: increased transcytosis, endothelial cell cytoplasmic channel formation, opening of a part of tight junctions, and free passage through the injured endothelium (with the higher power sonications of greater 3W). It was also demonstrated that the BBB opening size can be controlled by the acoustic pressure, i.e., at the greater acoustic pressure the larger are the molecules that can permeate through the BBB [55].

R. Alkins et al. [56] investigated the potential for focused ultrasound to deliver targeted NK-cells (natural killer cells) to the brain in animals with brain implanted metastatic breast cancer. The ratio of NK-cells to tumor cells increased from 1/1000 to 1/100 after exposure to ultrasound in the presence of microbubbles.

S. Wu, et al. [57] studied delivery of erythropoietin in rat brain after ischemia/reperfusion-induced neuronal injury. FUS sonication with microbubbles, significantly increased the cerebral content of erythropoietin, faster neurologic improvement and reduction of ischemia volume.

H. Liu et al. [58] in a mouse model showed that FUS sonication with microbubbles caused temozolomide accumulation in glioma to increase from 6.98 to 19 ng/mg. M. Kinoshita et al. [59] showed increased focused ultrasound-induced BBB permeability for delivery of Herceptin to the mouse brain. L. Treat et al. [60] using MRI-guided focused ultrasound with preformed microbubbles achieved significant increase in BBB permeability for doxorubicin in rats.

N. McDannold et al. [16] evaluated safety of enhanced BBB permeability by use of ultrasound and microbubbles on 7 rhesus macaques using the ExAblate 4000 system. 185 different functional regions of the brain were exposed. MRI and histological examinations made it possible to determine the effective intensity of the impact without evident tissue damage. The study demonstrated the possibility of predictable and reproducible local enhancement of BBB permeability in deep and surface targets. Follow-up and testing revealed no behavioral deficits, memory deficits, or loss in visual acuity.

The feasibility of using an implantable ultrasound system for enhancing permeability for carboplatin chemotherapy in patients with recurrent glioblastoma is under study [61].

Fig. 3. MRI with contrast before ultrasound thermal ablation (a, b, c) and 5 days after ultrasound thermal ablation (d, e, f) (from publication of D. Coluccia et al. [50]). Thermal destruction lesions are seen on control MRI in tumor that does not accumulate contrast agent.
Table 2. Different neuromodulating effects of focused ultrasound

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect</th>
<th>Description of the effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. Deffieux et al., 2013 [68]</td>
<td>Suppression</td>
<td>Increased time to perform an antisaccade task by trained macaque rhesus after sonication of the Brodmann area 8</td>
</tr>
<tr>
<td>S. Yoo et al., 2011 [67]</td>
<td>Stimulation</td>
<td>Emergence of motor responses at rabbit paws after sonication of the motor areas</td>
</tr>
<tr>
<td>S. Yoo et al., 2011 [67]</td>
<td>Suppression</td>
<td>Decrease of visual evoked potential value after exposure on visual areas</td>
</tr>
<tr>
<td>B. Min et al., 2011 [69]</td>
<td>Suppression</td>
<td>The occurrence of epileptic EEG bursts decreased and epileptic activity suppressed after sonication of the thalamic areas of the brain in rats</td>
</tr>
<tr>
<td>S. Yoo et al., 2011 [73]</td>
<td>Stimulation</td>
<td>Reduction of anesthesia duration in rats sonicated at the thalamic area</td>
</tr>
<tr>
<td>H. Kim et al., 2012 [74]</td>
<td>Stimulation</td>
<td>The eyeball initiated to roll forward at the abducens nerve sonication in rats</td>
</tr>
<tr>
<td>Y. Lee et al., 2015 [70]</td>
<td>Suppression</td>
<td>Conduction block of motor and sensory impulses on the sciatic nerve in rats when exposed to focused ultrasound</td>
</tr>
<tr>
<td>E. Tsirulnikov et al., 1988 [71]</td>
<td>Stimulation</td>
<td>Occurrence of hearing sensation in patients with hearing disorders (including deafness) and in normal hearing volunteers after sonication of the cochlea and the vestibulocochlear nerve</td>
</tr>
<tr>
<td>Y. Chung et al., 2014 [72]</td>
<td>Stimulation</td>
<td>Occurrence of sensations in the fingers and hands after sonication of the relevant somatosensory area in healthy volunteers</td>
</tr>
</tbody>
</table>

The potential of FUS to treat patients with neurodegenerative diseases, Alzheimer’s and Parkinson’s disease, is assessed in a large number of laboratories. J. Jordao et al. [62, 63] demonstrated that FUS increased β-amyloid antibody and endogenous antibody accumulation in plaques in transgenic mice with Alzheimer’s disease. Reduction of amyloid-β plaque size and number and glial activation were shown after ultrasound delivery. A. Burgess et al. [64] showed that FUS targeted to the hippocampus led to reduction of plaque number and size, activation of neurogenesis and spatial memory improvement in behavioral tests in a transgenic mouse model of Alzheimer’s disease.

Nondestructive neuromodulation

In contrast to high-intensity ultrasound, short pulses of low intensity ultrasound lead to reversible effects in nerve centers and conduction tracts [65]. Both laboratory animal studies and some recent preclinical studies have shown the ability of FUS to induce in vivo controlled neuromodulating, stimulatory and inhibitory, effects [66—74]. Low intensity ultrasound does not change the temperature in and around the target, as well as does not cause visible damage to tissues based on the results of histological studies. Examples of various FUS neuromodulating effects are shown in Table 2.

In combination with MRI (including functional MRI) low intensity ultrasound can be an invaluable tool for the study of nervous system physiology, as well as for diagnosing and treating a variety of diseases [75]. One of the potential applications is the search for new targets in functional neurosurgery. Preliminary identification of the target will then allow more effectively and safely carry out destructive interference or stimulation of deep brain structures.

There can be many more potential neuromodulating applications of ultrasound: increase in wakefulness level at depressed consciousness, epileptic activity arrest, blockage of pain impulses, and others.

Sonothrombolysis

Laboratory studies demonstrated the ability of focused ultrasound to destroy blood clots and thrombi. This effect is primarily associated with transient cavitation effect, i.e. rapid formation, growth, and collapse of microbubbles [76, 77].

Transcranial ultrasound had a beneficial impact on thrombi and improved recanalization of vessels after plasminogen activator injection [78]. J. Eggers et al. [79] demonstrated that ultrasound plus tissue plasminogen activator (modification of transcranial Doppler ultrasound) during an hour increases the frequency of full and partial recanalization from 22.2 to 57.9% (\(p=0.045\)). W. Culp et al. [80] demonstrated the feasibility to lyse cerebral clot rapidly in animal model using low-frequency ultrasound in combination with platelet-targeted microbubbles. Dissolution of clots in intracranial vessels after high intensity focused ultrasound alone was shown in another model [81].

In the case of intracerebral hemorrhage, focused ultrasound is effective and quick at liquefying the clotted blood and thereby facilitating minimally invasive evacuation of the clot. S. Monteith et al. [82] studied the feasibility of transcranial MR-guided focused ultrasound liquefying the clotted blood in animals and cadaveric models. These data support the feasibility of dissolution
and evacuation of more than 95% of the clot and absence of negative influence on the brain.

Treatment of ischemic and hemorrhagic strokes using focused ultrasound [83] is the next and new stage of development of this high-potential technology.

Conclusions

The use of focused ultrasound in diseases of the central nervous system seems a promising technique. With the latest technical solutions, the rapid development of this technology has occurred in the latest few years. Focused ultrasound, depending on the parameters, causes various biological effects, many of which can be used for diagnostic or therapeutic purposes. Some applications of the technology (thermal destruction of the target in the treatment of Parkinson’s disease, essential tremor, and others) are already used in medical practice in clinical trials, and in some countries the technology has been approved as a therapeutic modality.

Other effects are only at the implementation stage. For example, there is information about the use of focused ultrasound in oncology (thermal ablation of tumors, enhancement of BBB permeability for chemotherapy). Some techniques are only under study at laboratories (destruction of intracranial targets with the help of cavitation, nondestructive neuromodulation). Some applications of FUS are at an early stage of development and are only potentially considered for treatment of central nervous system diseases [84—86]. For example, the potential of sonodynamic therapy similar to photodynamic therapy is considered [84]. This technology before wide implementation faces significant technical, research, and clinical work. Nevertheless, so far we can witness the appearance of the new clinical tool that will supplement the existing surgical and radiation treatments for CNS diseases.

Authors declare no conflict of interest.

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