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### REVIEW

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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

- Head surgery in the pictorial art of the past
- Diffusion kurtosis imaging in diffuse axonal injury
- Fourth ventricle meningiomas
Proton (1H) magnetic resonance spectroscopy (MRS) is currently widely used in the diagnosis of brain diseases besides standard MRI techniques. This method is useful to analyze tissue metabolic features and determine relative (peak ratio) and absolute concentration of metabolites in various tissues [1—6].

Phosphorus (31P) MRS has become a new approach in the non-invasive assessment of cerebral metabolism [4, 6, 7]. This method is accompanied by new opportunities in the study of brain metabolism. 31P MRS uses the resonant frequencies of phosphorus nuclei (31P) in various chemical compounds and allows registering the following major metabolites: PME — phosphomonoesters, PDE — phosphodiesters, Pi — inorganic phosphate, PCr — phosphocreatine, ATP — adenosine triphosphate with three peaks αATP, βATP and γATP.

Clinical value of 31P MRS in neurology and neurosurgery is determined by crucial role of phosphorus-containing compounds in brain metabolism and their high concentration in white and gray brain matter. Therefore, non-invasive assessment of cerebral metabolic reactions is possible. Moreover, it is assumed that changed energy status of brain cells precedes their structural remodeling. 31P MRS is able to visualize pathological changes in brain tissue at the earliest stages of structural remodeling which can later be observed on structural images. In addition, an important aspect of phosphorus MRS is non-invasive pH measurement in brain matter in health people and patients with brain tumor [8—10].

The purpose of the study is clinical analysis of reproducibility and diagnostic value of phosphorus MRS for assessment of brain metabolism and intracellular pH measurement in intact brain matter.

Material and methods

There were 23 volunteers aged 21—28 years (15 men and 8 women, mean age 25 years). The study included young people without any clinical neurological symptoms and MRI-signs of brain diseases followed by anatomical abnormalities. The study protocol was approved by the ethics committee of the Burdenko Neurosurgery Center. All volunteers signed an informed consent. Phosphorus MRS was performed using a specialized dual-tuned 1H-31P coil. All examinations were performed using 3.0 T MRI scanner (GE). Target brain area 6×6×2 cm was chosen in the projection of hemispheres. This segment contained both white and gray matter, did not capture brain ventricles and great vessels. Area of semioval centers was the most common. Position of the region of interest was determined by strictly axial T2-weighted images (T2-WI). Region of interest (a) with phosphorus spectrum measurement (b) are shown in Fig. 1. Tissue signals outside the region of interest were suppressed us-

Abbreviations:

- PME — phosphomonoesters
- PDE — phosphodiesters
- Pi — inorganic phosphate
- PCr — phosphocreatine
- ATP — adenosine triphosphate with three peaks αATP, βATP and γATP
- 31P MRS — phosphorus (31P) MR-spectroscopy
- PCho — phosphocholine
- PEth — phosphoethanolamine
- GPE — glycerophosphaethanolamine
- GPC — glycerophosphocholine

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Evaluation of brain metabolism is an important part in examination of brain lesions. Phosphorus magnetic resonance spectroscopy opens up great opportunities for studying the energy metabolism and allows noninvasive examination of metabolic processes occurring both in healthy and in pathologic brain tissue by obtaining a spectrum of phosphorus-containing metabolites involved in the turnover of cell membrane phospholipids.

The technique presented in this paper was used to conduct 31P MR spectroscopy and to estimate the ratio between the peaks of the main metabolites and intracellular pH of the healthy brain tissue of 23 volunteers in the age group under 30 years old in clinical settings. Based on the recorded stable phosphorus spectra of metabolites of the healthy brain tissue, the value of intracellular pH (6.963±0.044) and the ratio of the main PME/PDE peaks (1.17±0.20) were calculated. The database was created to subsequently analyze the metabolic changes in brain tissue spectra in norm and in pathology, as well as the intracellular pH variations that have diagnostic and prognostic value.

Keywords: (31P) MRS, brain energy metabolism, intracellular pH.
High frequency (128 MHz) was used to increase magnetic field homogeneity inside the region of interest. Then, we adjusted the parameters of receiver coil at a phosphorus frequency (51.7 MHz) according to peak of phosphocreatine (frequency with high and narrow peak). Then, MRS was performed (data recording time — 12 min). However, total time of the study was up to 30 min due to prolonged initial setup of MRI scanner for phosphorus MRS. Phosphorus MRS data were processed using the SAGE (GE) software package. We have also calculated intracellular pH using the equation published by Petroff et al. [11]:

$$\text{pH} = 6.77 + \log \left( \frac{\delta \text{Pi} - 3.29}{5.68 - \delta \text{Pi}} \right),$$

where $\delta \text{Pi}$ — chemical shift of inorganic phosphate in relation to phosphocreatine peak. The definition of $\delta \text{Pi}$ is shown in Fig. 2.

The influence of chemical bonds on the local field results chemical shifts up to several tens of Hz, while values of resonant frequencies are several tens of MHz. Therefore, the values of chemical shifts are expressed as ppm (parts-per-million) which are independent of magnetic field magnitude of MRI scanner. Chemical shifts of compounds interesting for biological researches are within a rather narrow range of about 25 ppm on a scale from −10 to +15. We additionally calculated metabolic peaks ratio for assessment of phospholipid and energy metabolism. In these calculations, we used a standard approach of measurement of these ratios described in previous studies [8—11]. Statistica v.6 software package was used for statistical analysis. Differences were significant at p-value <0.05.

**Results**

In our sample, we have obtained a stable phosphorus spectrum of major metabolites peaks in intact brain matter, that confirmed the adequacy of MRS. Phosphorus spectrum of the brain of healthy volunteer is shown in Fig. 1b. Chemical shifts (expressed in Hz and ppm) of the main metabolites for phosphorus MRS in relation to PCr peak position are presented in Table 1.

We estimated intracellular pH, phospholipids integrity and metabolism of intact brain through comprehensive analysis of all ratios of the metabolites.

Values of intracellular pH and metabolite peak ratios in 23 volunteers are shown in Table 2. pH values were calculated using the equation (1).

**Discussion**

Phosphocreatine (PCr) is characterized by the highest central peak in phosphorus spectrum of healthy tissue. The phosphorus spectrum is calibrated so that phosphocreatine peak frequency is 0 ppm. Phosphodiester peak (PDE=3.6 ppm) is located on the left from the PCr peak. The main components of this peak (glycerophosphoethanolamine and glycerophosphocholine) are structural elements of cell membranes, and increased PDE values are observed in case of advanced degradation of cell membrane phospholipids [12]. The following peaks are inorganic phosphate (Pi=5.3 ppm) and phosphomonoesters (PME=7.1 ppm). PME peak includes MR-signals of glucose-6-phosphate, sucrose-6-phosphate, as well as other hexose-6-phosphates and membrane phospholipid precursors. These peaks partially overlap. Some authors [9, 10] separately describe certain metabolites as the main elements of PME peak (phos-
phosphocholine (PCho) and phosphoethanolamine (PEth)) and PDE peak (glycerophosphoethanolamine (GPE) and glycerophosphocholine (GPC)). In our study of volunteers, we reliably differentiated only GPE and GPC peaks which form a common PDE peak. Differentiation of individual peaks within PME peak was difficult. Therefore, we used only the highest integral values of two peaks (PME and PDE) without dividing into separate components in further comparison.

Three peaks of adenosine triphosphate (ATP) are to the right of the PCr peak. PCr and total ATP belong to high-energy phosphates, while PME, PDE and Pi — low-energy phosphates. Comparison of these values is often used in assessing brain metabolism. Phosphoric spectra are quantitatively evaluated by the ratio of metabolite peak height to the αATP peak height [13, 14] or by the ratio of the areas under peaks to the area under the αATP peak as the most stable in phosphorus spectrum.

Molecules of all metabolites, except ATP, contain one phosphorus atom. Therefore, each molecule has only one resonant frequency, i.e. results one peak in the spectrum. Peaks of several metabolites almost coincide in $^3$P-spectrum if there are several chemically similar phosphorus-containing molecules with similar resonance frequencies in the matter. So, it is very difficult to distinguish the signal of glucose-6-phosphate from fructose-6-phosphate or other hexose-6-phosphates (components of PME peak) during clinical MRI.

ATP is fundamentally different from the other compounds, because there are three phosphorus atoms in this molecule. Resonant frequencies of the nuclei of these atoms are different, so $^3$P-spectrum of ATP consists of three separate peaks. These peaks are clearly different from each other and always reproduced using clinical MR-scanners. Three peaks of ATP were clearly visualized in our study ($\gamma$ATP: $-2.6$ ppm, $\alpha$ATP: $-6.8$ ppm, $\beta$ATP: $-15.7$ ppm).

It should be remembered that metabolite concentration in MR-spectrum is proportional to height of the peak and area under peak [14]. A narrow and high peak does not necessarily determine higher concentration of metabolite compared with low wide peak [15]. In our study, primary analysis of phosphoric MR spectra implied recording peak heights and spectra normalization regarding $\alpha$ATP peak height (similarly to proton MRS where all comparisons are made regarding to creatine peak).

The main components of PME peak (phosphocholine (PCho) and phosphoethanolamine (PEth)) are precursors of membrane phospholipids and involved into biosynthesis of phosphoglycerides [9]. The main components of PDE peak (glycerophosphocholine (GPC) and

### Table 1. Frequencies and chemical shifts of the peaks of the main metabolites in brain phosphorus spectra in healthy volunteers

<table>
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<tr>
<th>Metabolite</th>
<th>Frequency, Hz</th>
<th>Chemical shift, ppm</th>
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<tbody>
<tr>
<td>PME</td>
<td>$351\pm8$</td>
<td>$7.1\pm0.2$</td>
</tr>
<tr>
<td>Pi</td>
<td>$251\pm3$</td>
<td>$5.3\pm0.2$</td>
</tr>
<tr>
<td>PDE</td>
<td>$153\pm3$</td>
<td>$3.6\pm0.2$</td>
</tr>
<tr>
<td>PCr</td>
<td>$0$</td>
<td>$0$</td>
</tr>
<tr>
<td>$\gamma$ATP</td>
<td>$-132\pm6$</td>
<td>$-2.6\pm0.2$</td>
</tr>
<tr>
<td>$\alpha$ATP</td>
<td>$-397\pm6$</td>
<td>$-6.8\pm0.2$</td>
</tr>
<tr>
<td>$\beta$ATP</td>
<td>$-853\pm8$</td>
<td>$-15.7\pm0.2$</td>
</tr>
</tbody>
</table>
Table 2. pH value and metabolite peak ratios regarding their height

<table>
<thead>
<tr>
<th>Metabolite peak ratios</th>
<th>PME/PDE</th>
<th>PDE/Pi</th>
<th>PME/Pi</th>
<th>PME/αATP</th>
<th>PDE/αATP</th>
<th>PME/PCr</th>
<th>PDE/PCr</th>
<th>PCR/αATP</th>
<th>PCR/Pi</th>
<th>αATP/Pi</th>
<th>pH</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1.17±0.20</td>
<td>1.02±0.10</td>
<td>1.18±0.15</td>
<td>1.04±0.13</td>
<td>0.91±0.10</td>
<td>0.33±0.05</td>
<td>0.28±0.05</td>
<td>3.22±0.32</td>
<td>3.64±0.40</td>
<td>1.13±0.12</td>
<td>6.963±0.044</td>
</tr>
</tbody>
</table>

glycerophosphoethanolamine (GPE)) indicate the products of cell membranes decomposition [5, 16]. PME/PDE ratio may be valuable to analyze membrane phospholipid metabolism, membrane synthesis rate and phospholipid turnover. Thus, this indicator may be a marker of malignancy, continued tumor growth or tumor response to the treatment [5, 17, 18]. Interestingly, our value of PME/PDE ratio (1.17±0.20) differed from the normal values given by D. Ha et al. (0.47±0.07) [9]. Perhaps, these differences may be caused by technical features of MR-scanners (3.0 T MR-scanner in our study and 1.5 T MR-scanner used by the colleagues). Another aspect is volume of target area of brain tissue.

In the group of healthy volunteers, intracellular pH was 6.963±0.04 (median 6.945, min 6.89, max 7.05). Mean pH in our study was lower compared to that in researches of D. Maintz et al., D. Ha et al., Wenger K. et al. (7.04±0.01, 7.07±0.1, and 7.017±0.026, respectively) [9, 10, 17]. However, their results are similar to maximum pH values in our study. Different age may be one of the possible reasons of various pH of healthy brain tissue besides technical features of equipment because cerebral pH changes over years [19]. Similar age of volunteers was observed in our sample that determined the same pH values in the majority of people.

One of the drawbacks of phosphorus MRS is difficult recognizing the peaks of numerous metabolites in studies in vivo. Thus, phosphomonoesters peak (PME) in vivo is formed by about 10 different chemical compounds. Their signals partially overlap with each other. Therefore, it is difficult to distinguish peaks of each metabolite. Another disadvantage is associated with artifacts in measurements. Artifacts may be caused by magnetic field heterogeneity, metal implants (for example, dental crowns), blood signals and movement. Moreover, there was a large area of imaging in our research due to technical features of phosphorus MRS of our MRI scanner. As a result, a mixed signal from both white and gray matter and from other structures (great vessels, cerebrospinal fluid in subarachnoid spaces) was recorded.

Standard deviation of chemical shift was 0.2 ppm in our study, i.e. MR-scanner setup ensured a stable position of the peaks of all metabolites in relation to phosphocreatine peak. However, different magnitudes of chemical shifts of individual peaks (in ppm) in relation to phosphocreatine are reported in the literature. In our opinion, this is caused by several factors. For example, R. Kamble et al. [12] used an MRI scanner 1.5 T to obtain the phosphorus spectrum. Other reasons are features of receiving coils and setup parameters of scanners with different algorithms for noise and artifacts suppression.

**Conclusion**

$^{31}$P MRS is an advanced non-invasive research method with highly reproducible results regarding spectrum of metabolites involved in the energy metabolism and metabolism of cell membrane phospholipids. Measurement of peaks of certain metabolites is valuable to analyze processes in both intact and abnormal brain tissue. Moreover, $^{31}$P MRS is useful for non-invasive measurement of intracellular pH in healthy people and in those with central nervous system disease. In the future, $^{31}$P MRS may be useful to study mechanisms of occurrence and development of various (especially neurodegenerative) brain lesions. However, further studies are required for clinical adaptation of this method and determination of its role in non-invasive diagnosis of various brain lesions. The second part of the research will be devoted to the analysis of data in patients with brain tumors.

The research was supported by the grant of the Russian Science Foundation No. 18-15-00337.

**REFERENCES**

Energy Status and Features of Neoplasms.

Phosphorus magnetic resonance spectroscopy (MRS) and other modalities may be used to determine tumor malignancy grade and biological features. Metabolite peak ratios, their height and integral values are valuable for analysis of cell energy metabolism and cell membrane phospholipid metabolism through visualization of two metabolites (PME and PDE). These metabolites reflect cell membrane synthesis and degradation and intracellular pH. The last parameter varies depending on severity of cellular metabolic disturbances and may be a marker of tumor response to chemotherapeutic and radiotherapy. 31P MRS combined with 1H-MRS and other modalities may be also used to determine tumor malignancy grade and biological features of neoplasms.

The author concluded that this technique may be further used to assess metabolic features of damaged brain tissue. It is essential in diagnostic searching, monitoring of tumor response to the treatment and determining the prognosis.

**Authors declare no conflict of interests.**
Quality of Life in Patients With Pituitary Adenomas in the Pre- and Postoperative Period

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Objective — to evaluate changes in quality of life in patients before and after the resection of pituitary adenoma.

Material and methods. A clinical study involved 42 patients with pituitary adenomas. The diagnosis was based on clinical laboratory data, findings of radiology imaging and instrumented tests. Pituitary adenomas were resected through the transsphenoidal approach. Patients’ quality of life was analyzed in the preoperative and early postoperative periods. Patients were aged 22—63 years (median age, 45 years). A specialized EORTC QLQ-C30 questionnaire developed by the Quality of Life Group of the European Organization for the Research and Treatment of Cancer was selected for evaluation of quality of life in the pre- and postoperative periods. This questionnaire has been used in many international clinical studies.

Results. The patients showed positive dynamics during the postoperative period according to all functional scales. Such symptoms as fatigue, pain intensity, frequency of nausea, vomiting and shortness of breath were reduced in patients after the surgery. Intestinal motility was postoperatively normalized in these patients (the frequency of diarrhea or constipation events was reduced). The sleeping pattern was normalized. The patients also noted that their expected financial difficulties became less pressing after the surgery. The score corresponding to patients’ overall wellbeing was improved. Progression of such symptoms as the loss of appetite was observed in patients after the surgery.

Conclusion. Pre- and postoperative evaluation of various quality of life parameters in patients with pituitary adenomas revealed that gross total resection of pituitary adenoma through the transsphenoidal approach improved patients’ quality of life.

Keywords: pituitary adenomas, quality of life.

Pituitary adenoma is a tumor of the endocrine system and associated with advanced or impaired secretion of hormones from the anterior pituitary gland. Moreover, clinical symptoms are resulted by the influence of the neoplasm on the surrounding anatomic structures [1].

According to statistics, about 3000 cases of pituitary adenoma de novo are observed in Russia and the CIS countries annually [2]. Pituitary adenomas occupy the third place among intracranial tumors (7.3—18% of all verified brain tumors). The majority of patients are employable (about 75%) [3].

The purposes of any mode of pituitary tumor treatment (surgery, medication or radiotherapy) are to normalize pituitary hormone secretion, to eliminate clinical manifestations of hormone hypersecretion, to reduce dimension of a large tumor affecting vital cerebral structures (or eliminate neoplasm), to avoid long-term recurrences and to preserve function of anterior pituitary gland [4].

There is an advanced experience of transsphenoidal surgery for pituitary adenoma [5—7]. An obvious advantage of endoscopic surgery for chiasmal-sellar tumors is available well-lighted panoramic view of this area [8]. This facilitates clear differentiation of anatomical structures, prevention of their injury and complete removal of tumors. The use of optical magnification, operating microscopes and endoscopes, microsurgical techniques in pituitary tumor surgery significantly improved surgical outcomes, reduced mortality rate, incidence of recurrences and intraoperative complications [4]. Application of optical magnification with different angles of view allows removal of tumors "from behind the corner" (including neoplasms located lateral to internal carotid artery) under direct visual control [9].

An important direction of modern medicine is analysis of quality of life of patients. Currently, the term “health-related quality of life” (HRQOL) is often used in medicine [10, 11]. At the end of the 20th century, WHO determined essential criteria of HRQOL. Modern HRQOL questionnaires are based on the correlations of questions and answers and subsequent summation of scores. There are general questionnaires aimed at assessing health of the population as a whole regardless of pathology and special ones for certain diseases. Each questionnaire has its own criteria and scales [12].

The purpose of this study is to analyze quality of life in patients before and after removal of pituitary adenoma.

Material and methods

There were 42 patients (25 women and 17 men aged 22—63 years) with a histologically confirmed diagnosis of pituitary adenoma. Mean age of patients was 43.95±11.3 years (median 45 years). Diagnosis was confirmed by clinical and laboratory data, radiological and instrumental survey. Transsphenoidal approach with endoscopic assistance was used in all patients.

MR-scans within sella turcica and Knosp Scale were used to determine grade of cavernous sinus invasion by pituitary adenoma [13]. Three were various grades in our
sample: Grade 0 (normal placement of internal carotid artery and venous spaces) in 14.3% of patients, Grade I (tumor penetrates through the medial tangential line but does not extend beyond the intracarotid line) in 83.3%, Grade II (adenoma penetrates beyond the intracarotid line but does not go beyond the lateral line) in 2.4% of patients.

We assessed type of resection in 3—6 months after surgery. Complete excision of the neoplasm was confirmed by absent MR-signs of residual tumor in all patients.

Clinical analysis implied anamnesis of disease, evaluation of laboratory, instrumental data, intraoperative features, postoperative quality of life of patients.

Quality of life was analyzed in preoperative and early postoperative period (5—7 days after surgery, before discharge).

Currently, there are various questionnaires for assessing the quality of life of patients with pituitary adenoma (Anterior Skull Base Questionnaire (ASBQ), Sino-nasal outcome test (SNOT-22), EORTC QLQ-C30). The ASBQ questionnaire includes 35 grouped questions characterizing productivity, motor activity, endurance, pain, emotions, and specific symptoms [14]. The SNOT-22 questionnaire includes 22 questions devoted to nasal discharge, nasal congestion, pain, dizziness, impaired smell/taste, sleep, emotional state and impairment of sustained attention [15].

The EORTC QLQ-C30 special questionnaire is similar to the above-mentioned questionnaires. It was established by the Quality of Life Group of the European Organization for Research and Treatment of Cancer [16]. This questionnaire is used in many international clinical studies. EORTC QLQ-C30 is highly sensitive and applicable to assess quality of life regardless type of cancer. The questionnaire consists of 30 questions and different scales: general health; 5 functional scales — physical, role, cognitive, emotional and social functions; scales of symptoms. Symptomatic scale includes fatigue, nausea/vomiting and pain. Moreover, EORTC QLQ-C30 includes 6 separate items — insomnia, loss of appetite, constipation, diarrhea, dyspnea, financial difficulties [17—19].

EORTC QLQ-C30 questionnaire implies assessment of patient’s health and quality of life by himself unlike ASBQ and SNOT-22 questionnaires. Therefore, we preferred EORTC QLQ-C30 questionnaire for our study.

Answers to the questions of each scale of the EORTC QLQ-C30 questionnaire were numerically ranged within 0—100. Thus, higher values of functional and symptomatic scales determined better function and less severity of certain symptoms and toxicity. Conversely, lower scores of general health scales meant higher patient’s assessment of his general health before and after surgery [19].

Two-staged statistical analysis of data was performed using licensed SPSS Statistics 22.0 program. The first stage included analysis of distribution in samples. The second stage implied calculation of mean and standard deviation (M±SD) or median and interquartile range (Me; 25/75) depending on type of distribution. Pearson χ²-test was used to compare qualitative variables.

Kolmogorov—Smirnov test was applied to verify distribution for analysis of quantitative variables. Two-sided Spearman’s rank correlation analysis was used to determine correlation strength in case of abnormal distribution of variables, two-sided Pearson correlation analysis (r) — in case of normal distribution. Significance of differences (p) was also evaluated between groups. Threshold p-value of null hypothesis significance was 0.05 [20, 21].

Results

Transphenoidal approach was chosen in study patients with pituitary adenoma. Radical removal of pituitary adenoma (total resection) was performed in all cases. Mean time of surgery was 33.57±9.96 min, time of anesthesia — 63.69±17.22 min.

Length of hospital—stay was 7.74±3.07 days. We have assessed performance status of patients using the Karnovsky and ECOG-WHO scales. Thus, it was revealed that all study patients corresponded to 90% by Karnovsky scale in the preoperative period (i.e. patient is capable for normal activity, there are minor symptoms or signs of disease) and ECOG-WHO score 1 (there are symptoms of disease, but state is similar to normal). Postoperative improvement and no complaints were noted in 7.1% of patients (100% by the Karnovsky scale, ECOG-WHO score 0) [22—24].

Complaints of patients at admission were analyzed. The main preoperative complaints were diffuse headache (69%), memory impairment (57.1%), visual disorders (42.9%). Dizziness (9.5%), localized headache (4.8%), nausea and pain in the joints (2.4%) were rarer. Acromegaly was noted in 31% of patients, hormonal dysfunction — in 11.9%. There was a correlation between age and preoperative pain syndrome: older age was associated with more significant pain syndrome (r=0.523; p=0.001).

Visual disorders were presented by impaired visual acuity. There was a correlation between impaired visual acuity and age (r=0.408; p=0.007). Preoperative complaints for reduced visual acuity were more common in older people. Moreover, visual fields loss (hemianopsia) was diagnosed too. Patients with homonymous hemianopia lost temporal visual field only on the left (left-sided hemianopsia). Preoperative homonymous hemianopsia was observed in 11.9% of patients, postoperative — only in 4.8%. Preoperative bitemporal hemianopsia was found in 19% of patients. In postoperative period this disorder persisted in 11.9% of patients.

Quality of life was evaluated before and after surgery using functional and symptomatic scales.
Positive postoperative changes were found in all functional scales. So, improvement of physical (from 89.7±11.7 to 94.7±8.9), role (from 85±22 to 94.5±15.8), cognitive (from 69.4±24.4 to 91.7±13.8), emotional (from 69±24.7 to 92.9±18.8, \( p<0.05 \)) and social (from 83.7±23.1 to 96±12, 7) function was observed after surgery (Figure).

Quality of life in patients with pituitary adenoma in accordance with functional scales (EORTC QLQ-C30).

There was reduction of fatigue (from 62.9±25.9 to 77.1±19.8), severity of pain syndrome (from 71.4±30.4 to 84.9±22), nausea and vomiting (from 95.6±12.3 to 96±9.6), dyspnea (from 86.6±24.5 to 90.5±22.4). Normal intestinal motility, reduced incidence of diarrhea (from 96.8±12.3 to 100) and constipation (from 90.5±18.4 to 95.3±13.9), sleep normalization (from 72.3±33.7 to 81.1±28.6) were observed after surgery. Moreover, patients noted decrease of their expected financial difficulties after surgery (from 89.7±23.9 to 98.4±7.1). Analysis of the reasons of reduced financial difficulties after surgery showed that patients experienced relief due to total removal of tumor and improved performance status. They were ready to begin their official duties in time without need for a long rehabilitation.

Patients emphasized progression of “loss of appetite” symptom after surgery (from 91.3±19.5 to 89.8±20.1). An improvement of performance status was observed (from 46.5±19 to 25.3±13).

Thus, we have identified positive tendencies in 14 out of 15 scales of the EORTC QLQ-C30 questionnaire. Significant positive result was obtained for emotional scale. Negative dynamics was observed only for one symptomatic scale — loss of appetite.

There were no intra- and postoperative complications.

Discussion

A correlation between general health scale and functional/symptomatic scales in postoperative period was determined. Higher personal postoperative assessment of health was noted in patients who were satisfied with their social status (\( r=0.350; p=0.023 \)) and in those with improved appetite (\( r=0.433; p=0.004 \)).

We concluded that transsphenoidal surgery results improvement of quality of life in patients with pituitary adenoma considering positive postoperative changes in 14 out of 15 scales of quality of life. We assume that these significant early postoperative improvements in quality of life may be due to an elevated emotional background. Patients were happy at discharge because the most important stage in their treatment (surgery) was over, tumor was benign and completely removed and there were no complications. So, patients could return to usual lifestyle faster than they planned prior to operation.

Literature data devoted to this issue were analyzed. Earlier, C. Andela et al. [25] studied quality of life in patients with pituitary adenoma. Their research enrolled...
The authors noted that surgical and pharmacological measures for pituitary adenoma improve quality of life, but do not normalize it.

Conclusion

Transsphenoidal surgery for total removal of pituitary adenoma results in an improved quality of life. Patients noted postoperative negative trend only for one symptom — loss of appetite. Higher personal postoperative assessment of health was noted in patients who were satisfied with their social status ($r=0.350; p=0.023$) and in those with improved appetite ($r=0.433; p=0.004$). A complete recovery and the absence of complaints after surgery were noted in 7% of patients (100% by the Karnovsky scale, ECOG-WHO score 0).

Authors declare no conflict of interests.

The purposes of any elective neurosurgical procedure are not only saving patient’s life and minimizing complications, but also ensuring satisfactory postoperative quality of life. In patients with pituitary adenoma this variable depends on visual disability: SEE project.

Comparison of patients before and after transnasal adenomectomy in this report revealed only one negative tendency among 42 patients — aggravation of appetite in the postoperative period. This is most likely to be associated with aggravation of secondary hypocorticism. It would be important to analyze this complication regarding pre- and postoperative hormonal status.

The article is certainly relevant, because quality of life is increasingly being used to evaluate surgical outcomes. However, the drawback of the research is assessment of patients’ status only in early postoperative period (until discharge). Perhaps, the authors obtained increased emotional background of patients in early postoperative period rather a real improvement of quality of life due to short follow-up. The authors themselves note that patients (and their families) are happy after surgery without...
serious complications and complete removal of benign neoplasm.

At the same time, according to the Burdenko Moscow Neurosurgery Center and other researchers, transnasal adenomectomy is followed by aggravation of quality of life within few weeks after surgery. Mucous membrane swelling after surgery disrupts nasal breathing during the day and night, temporary olfactory disorders, nose bleeds and other postoperative manifestations arise.

Moreover, certain physical limitations exist within few weeks after surgery. All measures followed by increase of intracranial pressure (exercise, bending, sneezing, straining) are contraindicated (in order to prevent postoperative liquorreha). Hypopituitarism and transient diabetes insipidus often occur or aggravate in early postoperative period. Hormonal alteration requires hormone replacement therapy within few weeks after surgery that also cannot noticeably improve the quality of life.

Therefore, in our opinion and according to various authors (E. McCoul. J Neurosurg. 2015; 123: 813-820), recovery of quality of life after transnasal surgery occurs only after 6 weeks. Therefore, it is advisable to investigate quality of life not only in early postoperative period, but also after 3, 6, 12 weeks, etc.

Nevertheless, the obvious advantage of this report is determined by orientation of various specialists (neurosurgeons, endocrinologists and other specialists) on the possibility of using various evaluation criteria in clinical practice.

P.L. Kalinin, A.N. Shkaruba (Moscow, Russia)
Investigation of the Metabolic Features of Primary Glioblastomas by 99mTc-MIBI SPECT/CT and Evaluation of Their Effect on Disease Prognosis


Burdenko Neurosurgical Institute, Moscow, Russia

Objective — to study the effect of metabolic characteristics of the tumor determined by 99mTc-MIBI single-photon emission computed tomography (SPECT) and various molecular genetic features on the outcomes of combination treatment of hemispheric glioblastomas.

Materials and methods. This single-center prospective cohort study involved 68 patients aged 25—78 years (38 males and 30 females) with primary glioblastomas. Hypermethylation of the promotor region of the MGMT gene was observed in 24 (42%) out of 57 patients. The IDH1 mutation was revealed in two (3.5%) patients. The catamnestic data were available for 66 out of 68 patients. The first SPECT/CT study was carried out before chemoradiation therapy; the second SPECT/CT study was performed after the chemoradiation therapy. In each study, quantitative measures were calculated for the early (15—30 min after the patient had received a radiopharmaceutical) and late (after 45—60 min) phases.

Results. The actuarial survival rates after 12 and 24 months were 69.6 and 29.1%, respectively. The median overall survival rate was 17.5 months (95% CI 12.9—20.3). Favorable prognostic factors for overall survival included the higher uptake index (UI) in the late phase compared to UI in the early phase of the first SPECT/CT study (p=0.0444), dynamics of changes in UI during the second SPECT/CT compared to baseline over 10% (p=0.0436), MGMT hypermethylation (p=0.0003), and duration of the period between surgery and initiation of chemoradiotherapy being <1 month (p=0.0008). No statistically significant correlations were revealed between the absolute UI values in the tumor and its molecular genetic features.

Conclusion. The 99mTc-MIBI SPECT/CT can be used to predict overall survival and to plan radiation therapy of glioblastoma as it is more readily available at primary healthcare facilities than amino acid PET.

Keywords: glioblastoma, 99mTc-MIBI SPECT/CT, metabolic activity, radiotherapy, survival rate.

Glioblastoma is the most malignant intracerebral tumor with predominantly astrocytic differentiation [1]. According to the CBTRUS American Register [2], the incidence of glioblastoma is 14.7% among all central nervous system (CNS) tumors and 47.7% among all brain malignancies. These tumors are more common in elderly men (median age 65 years) [2]. Overall survival ranged from 12 to 17.1 months despite modern advances in microsurgery, stereotactic radiotherapy and drug therapy [3, 4]. Clinical introduction of temozolomide resulted in 2.5-fold increase of 2-year survival (from 11 to 27%) [5]. According to prospective studies, bevacizumab in the chemoradiation therapy. In each study, quantitative measures were calculated for the early (15—30 min after the patient had received a radiopharmaceutical) and late (after 45—60 min) phases.

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Keywords: glioblastoma, 99mTc-MIBI SPECT/CT, metabolic activity, radiotherapy, survival rate.
tomography (SPECT) occurred due to high price and limited availability of PET. A much more available scanners for SPECT than PET in oncology clinics and general hospitals, convenient preparation of a radiopharmaceutical agent from a generator, no need for complex equipment and relatively low price of examination are advantages of SPECT as a competitive method for diagnosing metabolic active sites of high-grade glial tumors [17, 18]. 201Tl-chloride, 99mTc-methoxyisobutylisonitrile (MIBI), 99mTc-tetrofosmin, 123I-alpha-methyl-tyrosine and others are used as tumor-targeted drugs [19].

The mechanism of intensified accumulation of these drugs in glial tumors is multidirectional [19]. Their retention in glioblastoma cells indirectly reflects metabolic activity of the tumor and depends on proliferative activity (it is much higher at the early stages of division), perfusion (it is lower in hypoxic areas of tumor) and electrical gradient of cell membranes. The reverse process of agent release from the cell is significantly influenced by Pgp transmembrane glycoprotein and Bcl-2 proapoptotic protein of mitochondria. These compounds act as cationic pumps for active release of 99mTc-MIBI from the cells.

The purpose of this prospective single-center cohort study is to study the effect of SPECT-determined metabolic characteristics of tumor and various molecular genetic features on the results of complex treatment of hemispheric glioblastomas.

Material and methods

There were 68 patients (38 men and 30 women) with hemispheric glioblastomas who were treated at the Burdenko Neurosurgery Center in 2016—2018. All patients signed an informed consent. The research was approved by the ethical committee. Diagnosis was verified by microsurgical removal of tumor (65 (96%) patients) or stereotactic biopsy (3 (4%) patients). The date of surgery was taken as the date of diagnosis. Age of patients ranged from 25 to 78 years (mean 54 years).

Tumor specimens were harvested in 57 patients for molecular genetic examination. The genotyping of IDH1 R132H variant and detection of aberrant DNA methylation of promoter region of MGMT gene were carried out using real-time LNA-Taqman PCR technology (QuantiStudio 5 scanner).

Patients underwent combined chemo-radiotherapy with temozolomide 75 mg/m² in 36 days after neurosurgical intervention in accordance with ESMO/EORTC guidelines [20]. 3D conformal radiotherapy was performed using linear electron accelerators (Primus, Siemens, Germany, Novalis, BrainLab, Germany; True-Beam, Varian, USA) and individual system for head fixation by thermoplastic mask. The contouring of radiation targets and dosimetric planning was carried out according to our protocols at workstations with an appropriate software: Amfora, Russia; IPlan and Eclips, Germany.

There was a conventional radiation mode: 30 fractions by 2 Gy up to overall dose of 60 Gy. Accelerated fractionation was applied in 3 patients (15 fractions by 3 Gy up to overall dose of 45 Gy) according to the protocol for elderly patients [21].

99mTc-MIBI SPECT was performed using a single-photon emission CT-scanner with two detectors combined with a multislice CT-scanner. National lyophilisate "Technetri" (LLC "Diamed") and 99mTc eluate obtained from the GT-4K generator (11 GBq) (Karpov Research Institute of Physics and Chemistry) were used to prepare radiopharmaceutical agent. The following characteristics of SPECT imaging were applied: exposure time for one plane 30 s, resolution 128×128, 60 angles (rotation angle of detector around the axis of the scanner 3°) by 2 planes with an opposite arrangement of detectors. SPECT was immediately followed by CT to precise anatomical features and subsequently analyze data. Reconstruction and subsequent analysis of tomography data were carried out using Singo MI VA60C software package (Siemens, Germany). Image reconstruction was made using an iterative method with OSEM algorithm, isotropic voxel and axial resolution 128×128. Absorption and scattering of radiation in the patient’s body were considered. We used a regular zone of interest (sphere with a diameter of 1 cm) to calculate relative parameters. Agent accumulation index was defined as a ratio of maximum accumulation of 99mTc-MIBI in the tumor and its physiological accumulation within the vascular plexus of the third ventricle. Each SPECT study consisted of early (15—30 min after intravenous administration of the agent) and delayed phases (45—60 min). Similar examinations were performed 1—2 days before chemo-radiotherapy, on the last day of irradiation and in 3—6 months after the onset of drug therapy with temozolomide.

Late phase data of the first 99mTc-MIBI SPECT were used for planning of radiotherapy. Metabolic volume of glioblastoma was included into the Gross Tumor Volume (GTV) in dosimetric planning (Fig. 1). Certain difficulties occurred in contouring of glioblastoma located near the lateral ventricles due to adjacent foci of advanced accumulation of radiopharmaceutical drug in vascular plexuses.

Statistical analysis was performed using MedCalc software package (version 18.11). Kaplan-Meier overall survival analysis was carried out to evaluate survival depending on certain factor over the entire follow-up period. Kaplan-Meier survival curves were compared using log-rank test. We applied χ² test in order to observe between-group differences and calculate risk ratio (RR) and 95% confidence interval (95% CI). Differences were significant at p<0.05.
Results

Hypermethylation of MGMT gene promoter was observed in 24 (42%) out of 57 patients. IDH1 mutation was found in 2 (3.5%) patients. Thus, wild type of glioblastoma was the most common type of tumor (96.5%).

Time interval between surgery and chemo-radiotherapy onset ranged from 15 to 146 days (mean 36 days). Classical fractionation of irradiation was applied as a rule (94%): 30 fractions by 2 Gy up to overall dose of 60 Gy. Three patients aged 78, 74 and 72 years underwent radiotherapy with accelerated fractionation (15 fractions by 3 Gy up to overall dose of 45 Gy). Radiotherapy was not performed in one patient due to early local progression followed by urgent redo surgery.

Overall functional status of patients was assessed using the Karnovsky score (0—100%). Mean Karnovsky score was 80% (range 60—90%).

Follow-up data were available in 66 patients. Progression of the disease (local or distant recurrence) was evaluated using contrast-enhanced MRI in accordance with RANO (Response Assessment in Neuro-Oncology) criteria [22]. Date of control MRI was accepted as the date of recurrence. Local/distant recurrence occurred in 44 out of 68 patients. Mean recurrence-free survival was 7 months (95.5% CI 6.0—10.6). Local recurrence within postoperative bed was diagnosed in 95% of cases. Only 2 (4.5%) patients had distant recurrence, i.e. glioblastoma de novo occurred outside the 80% of isodose curve. Marginal recurrences (on the border of 95—80% of isodose curve) were not encountered in this study.

Actual 12- and 24-month survival was 69.6 and 29.1%, respectively. Median overall survival was 17.5 months (95% CI 12.9—20.3).

Accumulation index (AI) in the early phase of the first SPECT before chemo-radiotherapy ranged from 0 to 3.41 (median 0.48). In the late phase, this ratio decreased to 0.39, but maximum value increased up to 5.27. Dynamics of AI during the first examination (i.e., difference between late and early phases: IN60_1—IN30_1) was multidirectional. AI increased from early to late phase in 30 (44%) out of 68, decreased in 35% of observations and remained stable throughout the entire study in 14 (21%) out of 68 patients (including 10 patients without pathological accumulation of radiopharmaceutical in both phases of SPECT). Maximum release (i.e., decrease of IN60_1 compared with IN30_1) reached 49%, while accumulation of radiopharmaceutical from early to late phase was 192%. There was no significant correlation between absolute values of AI in any phase of the first SPECT and overall or disease-free survival in patients with primary glioblastoma. Favorable predictor of overall survival was increase of IN60 in the late phase compared with IN30 in the early phase of the first SPECT before chemo-radiotherapy (Fig. 2). Difference between IN60 and IN30 over 0 resulted median overall survival of 10.6 months (95% CI 6.08—26.96), whereas negative or equal to zero IN60—IN30 was followed by significantly lower survival — 6.4 (95% CI 4.64—9.57; p=0.0444).

The first SPECT-CT with 99mTc-MIBI in the early phase was used to correct GTV in dosimetric planning of stereotactic radiotherapy on a linear accelerator (Fig. 3). The prescribed isodose was applied to the entire PTV without the use of intensity modulation or integrated boost techniques.

Discussion

MRI may be performed only within 48 hours after surgery because this method becomes uninformative later due to breakdown products of hemosiderin. 99mTc-MIBI SPECT is valuable to visualize residual metabolically active glioblastoma in any time after surgery [19]. The mechanism of radiopharmaceutical drug accumulation for SPECT, including glial tumors, is not clear. Amino acids (methionine, dopamine, choline, tyrosine, etc.) used in PET are directly involved in metabolic processes in tumor cells. However, tropism and retention of 99mTc-MIBI in glial cell structures is complex and multidirectional process [23]. Accumulation of this radiopharmaceutical in a tumor directly depends on blood supply of glioblastoma: reduced accumulation of 99mTc-MIBI reflects hypoxia and, consequently, resistance of tumor to radio- and chemotherapy [24].

Median AI in the early phase of the first SPECT prior to chemo-radiotherapy was 0.48 (range 0—3.41). In the late phase, median AI decreased to 0.39, but maximum value increased up to 5.27. Dynamics of AI during the first examination (i.e., difference between late and early phases: IN60_1—IN30_1) was multidirectional. AI increased from early to late phase in 30 (44%) out of 68, decreased in 35% of observations and remained stable throughout the entire study in 14 (21%) out of 68 patients (including 10 patients without pathological accumulation of radiopharmaceutical in both phases of SPECT). Maximum release (i.e., decrease of IN60_1 compared with IN30_1) reached 49%, while accumulation of radiopharmaceutical from early to late phase was 192%. There was no significant correlation between absolute values of AI in any phase of the first SPECT and overall or disease-free survival in patients with primary glioblastoma. Favorable predictor of overall survival was increase of IN60 in the late phase compared with IN30 in the early phase of the first SPECT before chemo-radiotherapy (Fig. 2). Difference between IN60 and IN30 over 0 resulted median overall survival of 10.6 months (95% CI 6.08—26.96), whereas negative or equal to zero IN60—IN30 was followed by significantly lower survival — 6.4 (95% CI 4.64—9.57; p=0.0444).

The first SPECT-CT with 99mTc-MIBI in the early phase was used to correct GTV in dosimetric planning of stereotactic radiotherapy on a linear accelerator (Fig. 3). The prescribed isodose was applied to the entire PTV without the use of intensity modulation or integrated boost techniques.
Median Al in the early phase of the second SPECT after chemo-radiotherapy was 0.42 (range 0—7.29). In the late phase, median Al increased up to 0.5, but maximum value of IN60_2 decreased slightly to 6.59. Dynamics of Al during the second SPECT (i.e., difference between IN60_2 and IN30_2) was also multidirectional. Al increased or decreased from early to late phase in 45% of cases and was stable in 10% of patients (including 7 patients without pathological accumulation of radiopharmaceutical in both phases of the second SPECT). There was a correlation (Fig. 4) of Al dynamics in the late phase between the first and the second \[^{99m}Tc\text-MIBI\] SPECT. Median overall survival was significantly higher if IN60_2 was significantly greater or smaller than in initial examination. Worse survival was observed in patients with IN60_2 similar to zero, i.e. Al changes in the second study did not exceed 10% of the initial value (10.6 vs. 6 months; \(p=0.0436\)).

Reverse prognostic dependence of increased accumulation of \[^{99m}Tc\text-MIBI\] in primary glioblastoma and increase of Al after chemo-radiotherapy is due to two features of this radiopharmaceutical. First, fast release of this compound from the tumor is caused by transmembrane glycoprotein (Pgp) in tumor cell membranes. This glycoprotein works as a cation pump for active release of radiopharmaceutical from the cell. Secondly, proapoptotic Bcl-2 protein in the tumor cell prevents \[^{99m}Tc\text-MIBI\] accumulation in those cells of glioblastoma experiencing
apoptosis and hypoxia [23]. Both mechanisms determine tumor resistance to chemotherapy due to elevated level of Pgp. Resistance to radiotherapy is caused by resistant hypoxic areas in glioblastoma with cellular apoptosis.

According to large clinical trials, overall survival in patients with glioblastoma does not exceed 2 years despite modern achievements in microsurgery, radio- and chemotherapy (including administration of such drugs as temozolomide and bevacizumab). International randomized study RTOG 0525 (NCT01364064) [25] enrolled 833 patients with primary hemispheric glioblastomas for the period 2007—2011. Temozolomide 150—200 mg/m² was administered from the 1st to the 5th day of the 28-day cycle after combined chemo-radiotherapy in group 1, the same drug 75—100 mg/m² from the 1st to the 21st day — in group 2. Overall survival was 16.6 and 14.9 months in both groups. In the second trial RTOG 0825 (NCT00884741) [7], 637 patients with primary glioblastoma were randomized into two groups. In group 1, patients underwent combined chemo-radiotherapy (temozolomide + bevacizumab every 2 weeks after the 4th week of treatment. Chemo-radiotherapy with temozolomide alone was used in the control group. Median overall survival was 15.7 and 16.1 months, respectively. Prognostic role of MGMT gene methylation status was also shown in this study. Median overall survival in patients with unmethylated MGMT gene was 14.3 months, in those with hypermethylation of MGMT gene — 23.2 months.

In our trial, median overall survival was 17.5 months. In the majority of cases, the most adverse wild type of glioblastoma (without mutation in the 132nd codon of the IDH1 gene) and hypermethylated MGMT gene were observed. IDH1 gene mutation did not significantly influence median survival. Apparently, this is due to small sample size. IDH1 mutation was detected only in 2 (3.5%) out of 57 patients. Median age of patients with glioblastoma was 56 years in our sample (only 15 patients were younger 50 years old). However, it is known that IDH1/2 mutation is casuistic in patients older than 50 years [26]. In addition, some authors reported rarer hypermethylated status of MGMT gene in IDH1/2-mutant glioblastomas compared with gliomas grade II and III although IDH1/2 gene mutation is a favorable predictor [27, 28]. So, these tumors are less sensitive to alkylating chemotherapeutic drugs (temozolomide) [29].
ylation status of MGMT gene was a favorable factor in our research (Fig. 5). Median overall survival in patients with hypermethylated status was 27 months compared with 13.2 months in patients with unmethylated MGMT gene (p=0.0003).

In our trial, overall and disease-free survival in patients with primary glioblastoma was not significantly correlated with age, surgical strategy (removal or stereotactic biopsy), functional status by Karnovsky scale prior to chemo-radiotherapy or RPA class, fractionation mode of radiotherapy (conventional with 30 fractions or accelerated with 15 fractions), type of chemotherapy during irradiation (temozolomide alone or with bevacizumab). Apparently, this is also largely due to small sample size. For example, stereotactic biopsy was performed only in 3 (4%) out of 68 cases. Bevacizumab in the first line of chemotherapy was administered only in 3 (4%) out of 68 patients. However, overall survival significantly depended on time period between surgery and subsequent chemo-radiotherapy (p=0.0008) (Fig. 6). Delayed irradiation (over 1 month after surgery) resulted median survival of 13.2 months (95% CI 8.2—18.6), irradiation within 1 month after surgical treatment — 25.6 months (95% CI 19.2—27.25).

Median time to progression was 6.5 months in patients with unmethylated MGMT gene and 10.6 months in those with hypermethylated MGMT gene (p=0.0724). So, steady trend towards improved overall survival in patients with hypermethylated MGMT gene status was found despite insignificant differences. This can be explained by the fact that progression or recurrence of glioblastoma were confirmed by MRI data in our study as a rule (PET or SPECT for differential diagnosis of post-radiation changes and continued growth were carried out only in 6 out of 44 observations). Moreover, RANO criteria for tumor progression are not obvious in some aspects. For example, enlargement of contrast accumulation area by 25% and over may be clearly defined, while significance of increased T2 FLAIR hyperintense area may be evaluated differently [22, 30]. Moreover, pseudo-progression phenomenon deserves a special mention. It is a transient enlargement of contrast accumulation area in T1-weighted images within 12 weeks after chemo-radiotherapy [31]. This phenomenon occurs in 20—30% of cases (in patients with hypermethylated MGMT gene as a rule) [32]. In this regard, molecular imaging methods (PET with amino acids or SPECT) are currently recommended for differential diagnosis of post-radiation changes and continued growth of glioblastoma after chemo-radiotherapy. RANO/PET group was created in the European Association of Neuro-Oncology in order to clarify PET-criteria of progression of glioblastoma after chemo-radiotherapy.
Conclusion

Prognosis remains extremely unfavorable in patients with primary glioblastomas. Overall survival does not exceed 2 years. In this prospective series, median overall survival after microsurgical removal, stereotactic irradiation and modern chemotherapy was 17.5 months, median period until progression — 6.9 months. Significant predictive factors of overall survival were MGMT gene hypermethylation, time interval between surgery and che-}

mo-radiotherapy and increase of contrast accumulation from early to late phase during initial SPECT-CT prior to chemo-radiotherapy. 99mTc-MIBI SPECT may be used to predict survival and plan radiotherapy considering higher availability for primary oncological institutions in comparison with PET with amino acids.

Authors declare no conflict of interests.

REFERENCES


A single-center prospective cohort study is devoted to the topical issue. It is a searching for predictors of survival in patients with extremely malignant tumors (glioblastomas).

There was a relatively small group of adults with verified hemispheric glioblastomas who underwent complex treatment including surgery (stereotactic biopsy in only 2 cases) and chemo-radiotherapy. Molecular genetic studies including analysis of MGMT gene methylation status and IDH1 mutation were conducted in the majority of patients (57 out of 68). These examinations are determined by modern requirements for a complete histological study considering the latest edition of WHO recommendations and classification (2016). Authors’ data confirm positive relationship of methylated status of MGMT gene and survival prognosis. At the same time, radical removal of tumor, age and state of patients were not determined as significant predictors of life expectancy in patients with glioblastomas. Apparently, it is caused by small sample size.

Significant part of research is devoted to $^{99}$Tc-MIBI SPECT in refining tumor volume after removal, application of these data to plan radiotherapy and prognostic significance of $^{99}$Tc-MIBI accumulation/release. It is shown that these data may be used for radiotherapy planning, in case of impossible MRI on the first day after surgery and/or PET. The last techniques are preferred today, but associated with significant technical difficulties and economic problems. Advisability of $^{99}$Tc-MIBI SPECT for differential diagnosis of pseudo-progression of tumor after chemo-radiotherapy was established. The authors found significant relationship between accumulation characteristics and overall survival in patients with hemispheric glioblastomas. This is of great theoretical and practical importance and may be recommended for complex treatment of glioblastomas if PET with amino is impossible.

M. B. Dolgushin, A. Kh. Bekyashev (Moscow, Russia)

Commentary

ORIGINAL ARTICLES
The main diagnostic issues regarding monitoring of the treatment of patients with cerebral gliomas are early detection of continued tumor growth and its reliable distinction with brain changes as side effects of adjuvant treatment. Low specificity of conventional contrast-enhanced magnetic resonance imaging (MRI) requires additional diagnostic techniques to specify structural brain damage [1]. Positron emission tomography (PET) (or PET combined with computed tomography – PET/CT) with amino acids is used in functional neuroimaging for this purpose [2, 3]. We have previously identified the main types of brain damage after combined treatment of cerebral gliomas: 1) recurrent tumor, 2) radiation injury of the brain, 3) combined process including tumor with amino acids transport disturbances in patients with tumor progression.

The purpose of the study is to determine the role of $^{11}$C-methionine PET/CT (PET) in the diagnosis of continued growth of cerebral glioma using ROC-analysis. Moreover, the objective was comparison of relative incidences of three types of brain lesions at different $^{11}$C-methionine AIs.

**Material and methods**

According to the purpose of research, we identified $^{11}$C-methionine PET or PET/CT for the period 2005—2017 in patients with suspected continued tumor growth in the database of our laboratory. Inclusion criteria were patient’s age 15 years and older, verified cerebral glial tumor, complex treatment with radiotherapy and MRI-signs of progressive structural brain damage (progressive contrast enhancement of tumor bed or other areas). Minimum time period after radiotherapy should have been 3 months in order to exclude patients with pseudo-progression. There were 318 patients with diagnosis confirmed by histological, clinical and radiological data. Moreover, we enrolled 6 patients with suspected radio-induced brain tumor after combined treatment of extracranial neoplasms of soft tissues of the head or extracranial areas. According to the purpose of research, we identified $^{11}$C-methionine PET or PET/CT in 324 patients suspected for continued growth of cerebral tumor based on magnetic resonance imaging (MRI) findings. A quantitative analysis of the results included calculation of the $^{11}$C-methionine uptake index (UI).

A ROC analysis revealed that the specificity of PET in the diagnosis of continued tumor growth (CTG) was 98%, and the sensitivity was 71% for a UI of more than 1.9. We found that 98% of lesions with a negative level of RP uptake were related to radiation brain lesions (RBLs) or residual tumors combined with radiation pathomorphisms. The UI in a range of 1.2—1.6 in 75% of lesions characterized a stable disease, but 25.5% of the lesions represented continued glioma growth. The proportion of recurrences increased to 40% in a UI range of 1.6—1.9, and 95.5% of brain lesions with a UI of more than 1.9 were tumor recurrences. Therefore, high $^{11}$C-methionine uptake with the UI above 1.9 in brain lesions characterized by radiological signs of disease progression is a highly specific indicator of CTG; however, the UI may significantly vary during tumor growth, and a substantial fraction of recurrent gliomas may have lower radiopharmaceutical uptake. In the case of borderline UI values, early dynamic control or complementary additional MRI or CT techniques should be used.

**Keywords:** continued tumor growth, radiation-induced brain injury, ROC analysis, $^{11}$C-methionine uptake index.
A hybrid PET/CT GeminiTF Base system (Philips) is currently used. This system includes PET-scanner combined with 16-slice CT-scanner.

The first stage implied CT in a low-dose mode. These data were used for correction of gamma quanta for attenuation and for binding metabolic changes to anatomical structures through programmatic combining the results of both methods.

Examination was started in 10 min after 11C-methionine 6—12 mCi administration. Duration of scanning was 20 min for mono-PET and 10 min for PET/CT.

Data were analyzed using workstations of the scanners. We used additional software Philips IntelliSpace Portal for comprehensive analysis of PET/CT data. This software package allowed combining PET and MRI data. Then, this information was used to determine whether 11C-methionine capture violations correspond to contrast-enhanced MRI-foci if it was necessary and technically possible. Quantitative analysis implied 11C-methionine AI which was determined as a ratio of radiopharmaceutical concentration in target area to this value in the reference region. A 8—10-mm area of interest was outlined within the site of maximum accumulation of radiopharmaceutical in the pathological focus. Reference area

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**Table 1. Characteristics of patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean ± standard deviation), years</strong></td>
<td>41±13 (40)</td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>154</td>
</tr>
<tr>
<td>female</td>
<td>170</td>
</tr>
<tr>
<td><strong>Treatment, n (%):</strong></td>
<td></td>
</tr>
<tr>
<td>surgery RT+CT</td>
<td>193 (60)</td>
</tr>
<tr>
<td>surgery + RT</td>
<td>43 (13)</td>
</tr>
<tr>
<td>STB+RT+CT</td>
<td>25 (8)</td>
</tr>
<tr>
<td>RT+CT</td>
<td>16 (5)</td>
</tr>
<tr>
<td>repeated irradiation + CT + surgery</td>
<td>47 (14)</td>
</tr>
<tr>
<td><strong>Time period after RT (median, min—max), n (months):</strong></td>
<td></td>
</tr>
<tr>
<td>continued growth of glioma (n=150)</td>
<td>16 (4—107)</td>
</tr>
<tr>
<td>radiation-induced brain injury (n=89)</td>
<td>12 (4—137)</td>
</tr>
<tr>
<td>combined brain lesion (n=85)</td>
<td>11 (4—75)</td>
</tr>
<tr>
<td><strong>Histological diagnosis, n (%):</strong></td>
<td></td>
</tr>
<tr>
<td>glioma grade II</td>
<td>88 (27)</td>
</tr>
<tr>
<td>glioma grade III</td>
<td>99 (31)</td>
</tr>
<tr>
<td>glioma grade IV</td>
<td>127 (39)</td>
</tr>
<tr>
<td>unverified glioma</td>
<td>4 (12)</td>
</tr>
<tr>
<td>extracranial tumor</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>arteriovenous malformation</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td><strong>Final diagnosis, n. (%):</strong></td>
<td></td>
</tr>
<tr>
<td>continued growth of glioma (n=150):</td>
<td></td>
</tr>
<tr>
<td>histological</td>
<td>70 (47)</td>
</tr>
<tr>
<td>MRI and PET data</td>
<td>60 (40)</td>
</tr>
<tr>
<td>clinical-radiological/death within 6 months</td>
<td>18/2 (13)</td>
</tr>
<tr>
<td><strong>Radiation-induced brain injury (n=89):</strong></td>
<td></td>
</tr>
<tr>
<td>histological</td>
<td>8 (9)</td>
</tr>
<tr>
<td>MRI and PET data</td>
<td>78 (88)</td>
</tr>
<tr>
<td>clinical-radiological (only for AVM)</td>
<td>3 (3)</td>
</tr>
<tr>
<td><strong>Tumor combined with radiation-induced brain injury (n=85):</strong></td>
<td></td>
</tr>
<tr>
<td>histological</td>
<td>23 (27)</td>
</tr>
<tr>
<td>MRI and PET data</td>
<td>62 (73)</td>
</tr>
<tr>
<td><strong>Follow-up period (min—max), months:</strong></td>
<td></td>
</tr>
<tr>
<td>continued growth of glioma (n=116)</td>
<td>18 (2—96)</td>
</tr>
<tr>
<td>radiation-induced brain injury (n=83)</td>
<td>11 (2—79)</td>
</tr>
<tr>
<td>combined brain injury (n=84)</td>
<td>24 (6—96)</td>
</tr>
<tr>
<td><strong>Outcome (continued tumor growth/tumor control), n (%):</strong></td>
<td></td>
</tr>
<tr>
<td>continued growth of glioma (n=116)</td>
<td>89/27 (77/23)</td>
</tr>
<tr>
<td>radiation-induced brain injury (n=82)</td>
<td>17/65 (21/79)</td>
</tr>
<tr>
<td>combined brain injury (n=84)</td>
<td>33/51 (39/61)</td>
</tr>
</tbody>
</table>

**Footnote.** RT — radiotherapy, CT — chemotherapy, STB — stereotactic biopsy.
was accepted as a similar area in the cortex of contralateral hemisphere.

L-methyl-[11C]-methionine ([11C]-methionine) was obtained in the radiochemical laboratory of the Institute through on-line [11C]-methylation of L-homocysteine thiolactone hydrochloride (lactone). This process was made on a cartridge with a sorbent for solid-phase extraction tC18 according to the previously described procedure [6]. Synthesis of [11C]-methionine was carried out on a completely automated module designed in the Human Brain Institute of RAS.

Verification of PET data. Final diagnosis was based on histological data after redo surgery (n=101), dynamic MRI and PET control (n=200) and combination of MRI and PET data (n=23). Thus, three variants of brain damage after combined therapy were identified: continued tumor growth, radiation-induced brain injury and tumor combined with radiation-induced pathomorphism of tissue.

Continued tumor growth was confirmed by the following criteria: histological verification after resection or biopsy; increased [11C]-methionine capture and contrast enhancement in the next control survey; effective repeated treatment of tumor, in particular, redo radiotherapy; full compliance of negative diagnostic pattern and high metabolic activity in a single study.

Radiation-induced brain injury was histologically verified after surgery only in few cases. Histological examination showed extensive areas of necrosis, brain tissue with astrocytic gliosis, lymphoid infiltration, hyalinized vessels without clear areas of tumor tissue. In the majority of cases, the diagnosis was confirmed by stable low metabolic activity in follow-up for at least 6 months for gliomas grade III—IV and 12 months for gliomas grade I—II and no obvious MRI-signs of residual tumor. Early radiological picture was characterized by gradual regression or increase of contrast enhancement. However, subsequent stabilization or reduction up to disappearance of contrast enhancement were obligatory. Previously initiated chemotherapy was continued within follow-up or patients were under dynamic observation with corticosteroids prescription. Bevacizumab was used in 10 patients. Partial or complete regression of contrast enhancement in monotherapy with bevacizumab (in case of insufficiently effective corticosteroid therapy) did not contradict the notion of radiation-induced necrosis in case of prolonged remission after withdrawal of targeted therapy and stable negative PET data in the area of interest.

Combination of tumor and radiation-induced necrosis was confirmed by morphological examination or clinical, radiological and metabolic features of disease. Typical characteristics of tissues were radiation-induced pathomorphism (fibrosis, extensive necrosis, chronic inflammation, calcification) and areas of glial tumor with nuclear and cellular polymorphism. Combined lesion suggested MRI of residual glioma (with or without contrast enhancement). This type was characterized by PET-data of increased capture of [11C]-methionine.

All cerebral foci were additionally divided into 2 groups for ROC-analysis: continued tumor growth and no continued tumor growth. Six foci of combined lesion were classified as continued tumor growth considering histological examination after redo surgery. Biopsy revealed glioma with extensive radiation-induced necrosis. Moreover, Ki-67 antigen expression over 5% was observed in 4 patients. Other combined lesions were stable residual tumor and radiation-induced brain injury. The absence of tumor growth progression should have been confirmed by subsequent PET and MRI within 6 months and later. These examinations had to confirm stable or regressing metabolic and radiological characteristics of lesion.

Statistical analysis included descriptive statistics for all variables and non-parametric criteria for comparison of groups. ROC analysis was used to clarify diagnostic value [11C]-methionine AI in the diagnosis of continued growth of glioma. Data were analyzed using Statistica 10 and MedCalc 12.3.0.0 software package.

**Results and discussion**

There were 326 contrast-positive foci in 324 patients because foci in both hemispheres were considered separately due to their different genesis in 2 patients. According to the final diagnosis, all lesions were divided into 3 main groups:

1) continued tumor growth — 150 (46%) foci;
2) radiation-induced brain injury — 90 (28%) foci;
3) combination of tumor and radiation-induced brain injury — 86 (26%) foci.

Descriptive statistics of radiopharmaceutical capture intensity in all groups is shown in Table 2.

Low AI of [11C]-methionine was typical for radiation-induced brain injury, high — for continued tumor growth. Intermediate values were characteristic for combined lesions. There were significant differences in AI between all groups (p=0.0001, Kruskal—Wallis test).

| Table 2. [11C]-methionine AI in three groups of brain lesion |
|-----------------|-----------------|-----------------|-----------------|
| Lesion                       | Mean and standard deviation | Statistical variable |
|                             | median           | 10—90th percentile | AI range        |
| Radiation-induced lesion (n=90) | 1.18±0.28    | 1.00             | 1.0—1.53        | 1.0—2.6         |
| Continued tumor growth (n=150) | 2.36±0.81    | 2.15             | 1.48—3.60       | 1.18—5.1        |
| Combined lesion (n=86)       | 1.54±0.28    | 1.51             | 1.23—1.87       | 1.0—2.70        |
ROC analysis was performed for both the entire sample and patients with glial tumors in order to determine the value of $^{11}$C-methionine AI in the diagnosis of continued tumor growth, i.e. patients with AVM and extracranial tumor were excluded. $^{11}$C-methionine accumulation index over 1.88 turned out to be the optimal threshold value to differentiate continued tumor growth and stable disease (Fig. 1a). In patients with gliomas, optimal threshold $^{11}$C-methionine accumulation index decreased up to 1.70 (Fig. 1b). Changes of AI threshold value were associated with changes of sensitivity and specificity. Reduced AI resulted in increased sensitivity and decreased specificity (Table 3).

### Analysis of $^{11}$C-methionine AI in 3 groups of cerebral lesion

Individual features of $^{11}$C-methionine capture after combined therapy of cerebral glioma were analyzed. For this purpose, all AI values were grouped into 4 intervals considering data of ROC analysis. Relative frequencies of 3 possible variants of cerebral lesion were calculated within each interval (Table 4). Incidences of 3 types of cerebral lesion were significantly different depending on

![Fig. 1. ROC-analysis of $^{11}$C-methionine accumulation index for differentiation of continued tumor growth and stable tumor process.](image)

**Table 3. Sensitivity and specificity of PET for various threshold values of $^{11}$C-methionine AI**

<table>
<thead>
<tr>
<th>Threshold AI value</th>
<th>Entire sample (sensitivity, specificity)</th>
<th>Only patients with gliomas (sensitivity, specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.43</td>
<td>92.00/63.50</td>
<td>92.14/64.63</td>
</tr>
<tr>
<td>&gt;1.65</td>
<td>80.58/86.23</td>
<td>80.00/86.59</td>
</tr>
<tr>
<td>&gt;1.7</td>
<td>77.70/92.22</td>
<td>77.14/91.46</td>
</tr>
<tr>
<td>&gt;1.88</td>
<td>71.22/97.60</td>
<td>70.71/97.56</td>
</tr>
</tbody>
</table>

**Table 4. Incidence of 3 types of brain lesion for various AIs of $^{11}$C-methionine**

<table>
<thead>
<tr>
<th>AI range</th>
<th>Radiation-induced brain lesion, $n$ (%)</th>
<th>Continued tumor growth, $n$ (%)</th>
<th>Tumor combined with radiation-induced brain lesion, $n$ (%)</th>
<th>In all, $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less 1,2</td>
<td>58 (92)</td>
<td>1 (2)</td>
<td>4 (6)</td>
<td>63 (100)</td>
</tr>
<tr>
<td>1,2—1,6</td>
<td>26 (26.5)</td>
<td>24 (24.5)</td>
<td>48 (49)</td>
<td>98 (100)</td>
</tr>
<tr>
<td>1,6—1,9</td>
<td>4 (7.5)</td>
<td>21 (39.5)</td>
<td>28 (53)</td>
<td>53 (100)</td>
</tr>
<tr>
<td>Over 1,9</td>
<td>2 (2)</td>
<td>104 (93)</td>
<td>6 (5)</td>
<td>112 (100)</td>
</tr>
<tr>
<td>In all</td>
<td>90 (28)</td>
<td>150 (46)</td>
<td>86 (26)</td>
<td>326 (100)</td>
</tr>
</tbody>
</table>
the metabolic index \( p = 0.0001 \), Person Chi-square test). According to Table 4, MR-contrasting phenomenon had radiation-induced genesis in 92% of cases of negative accumulation of \(^{11}\)C-methionine. Radiopharmaceutical capture was not increased at initial stage of continued tumor growth in 1 case. In case of combined lesion, negative radiopharmaceutical uptake in residual cystic-solid component of glioma indicated complete metabolic response of tumor to the treatment. AI range of 1.2—1.6 characterized either a combination of glioma with radiation-induced necrosis or radiation-induced injury in 75% of cases. However, this value could be associated with initial progression of glioma. AI range of 1.6—1.9 was typical for combined lesion, but almost 40% of lesions were classified as continued tumor growth. Interestingly, radiation-induced necrosis after radiotherapy for AVM and extracranial tumor (i.e. without tumor substrate) was characterized by increased uptake of \(^{11}\)C-methionine (AI over 1.5). Foci with AI over 1.9 were classified as continued tumor growth in 93% of cases. Tumor component of combined lesion was characterized by high metabolic activity, that was also considered as tumor progression.

Sample dividing into two groups (progressive or stable disease) revealed similar outcomes with minor differences due to variability of the final classification of combined lesions (Fig. 2). Examples of ambiguous PET/CT data are presented in Fig. 3 and 4.

Thus, our research showed the features of differential \(^{11}\)C-methionine PET diagnosis of continued growth of cerebral glioma and radiation-induced brain injury. Area under ROC curve (0.913) indicates a high diagnostic value of PET. However, the method is characterized by relatively low sensitivity. In other words, significant percentage of recurrent gliomas (especially at initial staged of continued growth) has a lower \(^{11}\)C-methionine uptake. Therefore, comprehensive analysis of \(^{11}\)C-methionine uptake intensity in recurrent gliomas and other brain lesions after combined treatment was required. As expected, progressive MR-contrasting or contrast enhancement de novo without increase of radiopharmaceutical accumulation was usually associated with radiation-induced genesis of negative radiological picture. In turn, the same MRI pattern of progressive cerebral lesion combined with increased uptake of radiopharmaceutical and AI over 1.9 determined continued tumor growth. These obvious differences in PET-semiotics of continued tumor growth and radiation-induced brain injury are valuable to differentiate these processes with typical manifestations. However, both types of lesion are characterized by certain variability of metabolic characteristics, while combined lesions are characterized by additional difficulties.

Fig. 2. Incidence of tumor progression and its control depending on \(^{11}\)C-methionine uptake.
Fig. 3. Continued growth of anaplastic astrocytoma in the left parietal lobe.

A 60-year-old woman has been diagnosed a small focus of contrast enhancement in the wall of postoperative cyst in 25 months after combined treatment (surgery, chemo- and radiotherapy) of anaplastic astrocytoma of the left parietal lobe (a). There were PET data of tangential slightly increased accumulation of 11C-methionine (AI=1.1) as a sign of low metabolic activity of residual tumor. It was more typical for radiation-induced injury (b, arrow). Contrast-enhanced area on MR-scans (c) and increased accumulation of 11C-methionine (AI=2.1) were found after 6 months (d). Considering these data, negative changes caused by continued tumor growth were supposed.

in their interpretation. Tumor cells or even continued tumor growth with simultaneous radiation-induced necrosis are frequently mentioned in histological studies [7—9]. In these cases, both subcomponents of lesion affect 11C-methionine uptake intensity and its spatial distribution inside the focus. Residual tumor was usually characterized by moderately increased uptake of radiopharmaceutical during PET, i.e. 11C-methionine uptake was negative in extremely rare cases of combined lesion. Analysis showed that moderately increased accumulation of 11C-methionine within the area of interest can have a different genesis. Slightly increased AI of 11C-methionine within 1.2—1.6 was usually associated with radiation-induced injury or residual tumor without proliferative activity. Nevertheless, almost 1/4 of lesions with these values of AI were represented by growing tumor. Low 11C-methionine uptake could be observed in small recurrent glioma, that may be partly explained by early diagnosis.
and partial mass-effect. A rare variant was continued growth of glioma with predominant necrotic component and, probably, low density of tumor cells. A ring-shaped pattern of increased 11C-methionine uptake with AI of 1.6 may be difficult for interpretation. This pattern is observed in case of tumor progression with predominant necrotic component and radiation-induced necrosis in the tumor. Intraoperative biopsy during resection usually found fragments of altered brain tissue, tumor and necrosis. Even histological examination is not always absolutely clear to determine the role of particular subcomponent in clinical picture and prognosis of disease [10]. However, presence of tumor cells usually supposes continued tumor growth. Assessment of proliferative activity and further course of disease may be essential. Increased uptake of radiopharmaceutical with AI 1.6—1.9 is the most difficult for interpretation in single examination. Incidences of recurrent tumor and residual tumor combined with radiation-induced necrosis were similar in these cases. Considering our own experience, we offer two

Fig. 4. Radiation-induced lesion of the left cerebellar hemisphere.
Contrast enhancement on MR-scans occurred in 12 months after surgery and radiotherapy for astrocytoma grade II of the left cerebellar hemisphere (a). PET revealed focal increase of 11C-methionine accumulation (AI=1.5) of the same localization. So, tumor growth could not be excluded (b, arrow). Control survey 4 months later found a partial regression of contrast enhancement (c) and initial decrease of radiopharmaceutical uptake intensity (AI=1.3) (d). Follow-up data confirmed radiation-induced lesion and absence of tumor progression.
main ways to solve diagnostic dilemma in case of this PET pattern:

1. Repeated PET/CT after 1—3 months depending on histological structure of glioma. Increase of $^{11}$C-methionine uptake and dimensions of metabolic abnormality is expected in case of tumor growth.

2. Complementary perfusion examination during CT or MRI. Analysis of local hemodynamic features in the area of interest contributes to a more accurate interpretation of lesion.

Conclusion

High $^{11}$C-methionine uptake with AI over 1.9 according to contrast-enhanced MRI focus is highly specific PET/CT sign of continued growth of glioma. At the same time, about 1/3 of recurrent gliomas were characterized by lower fixation of radiopharmaceutical. Control MRI and PET as soon as possible or additional radiological diagnostic techniques are advisable in case of intermediate AI of $^{11}$C-methionine.

Authors' participation:

Concept and design of the study — T.S.
Collection and analysis of data — A.G., Zh.S., T.S.
Statistical analysis — T.S.
Writing text — T.S.
Editing — A.G., Zh.S.

Authors declare no conflict of interests.

REFERENCES


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Commentary

The article of T.Yu. Skvortsova et al. is devoted to an actual problem in the treatment of brain tumors, which is interesting for neurosurgeons, neurologists and specialists for neuroimaging. Relevance of differential diagnosis of continued growth of brain tumors and radiation-induced lesion is obvious. Various adequate technologies for differential diagnosis are searched in clinical practice. There are well known publications devoted to MR and CT perfusion techniques as the most common and available in the clinic [1]. Qualitative, semi-quantitative and quantitative threshold values of various numerical indicators are developed and proposed in these researches in order to describe various pathological changes with different specificity and accuracy. In this paper, the authors appeal to diagnostic PET-CT with methionine. This radiological technology requires the use of certain methods and specialized equipment for production of radiopharmaceuticals. Therefore, this method is still less common compared with CT and MRI but characterized by the unique properties. These advantages are absent in the above-mentioned technologies. PET is especially valuable for differential diagnosis of tumor growth and radiation-induced necrosis. The authors have accumulated and analyzed clinical data of unique quantity and quality — 1167 PET studies with methionine in 324 patients. The authors statistically analyzed their data and assessed specificity and sensitivity of selected threshold values of radiopharmaceutical accumulation index. These measures were valuable to differentiate continued growth and radiation-induced brain injury or assume combined lesion (i.e., presence of tumor and post-radiation response) in contrast-enhanced area revealed by previous MRI.

Obviously, the research is relevant and important for clinical practice. However, certain shortcomings should be considered. In particular, the authors analyzed diagnostic data obtained on different PET-CT scanners. Researchers did not evaluate and discuss resolution of equipment, while these features could affect the final quantitative results. Authors transferred region of interest to the cortex of contralateral hemisphere (as a reference zone). This area had very small dimension (8—10 mm), that significantly reduced signal-to-noise ratio and could affect quantitative results too. The most significant disadvantage is combination of low (88 cases) and high (99 and 127 cases) grade gliomas into general group without information about preoperative AI. It is well known that low grade gliomas with initially small AI can show significant variations of this value depending on histological type. So, oligodendroglioma usually has higher methionine uptake than, for example, astrocytoma with diffuse growth. At the same time, the authors discussed in detail advantages and some drawbacks of PET with methionine in differential diagnosis of continued growth and post-radiation response and suggested their own additional examination algorithm to clarify the diagnosis.

The research is of great interest for neurosurgeons and specialists for neuroimaging. The authors’ data may be used in clinical practice considering above-mentioned remarks.

I.N. Pronin (Moscow, Russia)

REFERENCES

Stereotactic Radiosurgery in Treatment of Trigeminal Neuralgia

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Summary: Stereotactic radiosurgery can be used to alleviate pain in most patients with type 1 trigeminal neuralgia, but its results are inferior to those of invasive interventions. According to our findings, 18% of patients had a relapse. For patients with multiple sclerosis accompanied by type 2 and symptomatic trigeminal neuralgia, this method is not sufficiently effective. When both microvascular decompression and stereotactic radiosurgery can be used to treat type 1 and 2 trigeminal neuralgia, patient’s choice is crucial. It is important to inform the patient both about the potential complications of the interventions and about the delayed effect of the surgery and relapse frequency.

Keywords: trigeminal neuralgia, Gamma knife, stereotactic radiosurgery.

Trigeminal neuralgia (TN) is a syndrome characterized by paroxysmal acute or burning pain in the area of trigeminal nerve innervation. Highly intensive facial pain significantly reduces quality of life, impedes labor activity, causes depression and suicidal thoughts. Various drugs are used to relieve pain, but medication is not always effective. In these cases, different surgical techniques (open or percutaneous) may be applied.

Currently, the “gold standard” of surgical treatment of TN is microvascular decompression aimed at correction of neurovascular conflict if it is present. Unlike other methods, these operations imply disjunction of TN and compressive vascular loop rather nerve destruction. Microvascular decompression results fast, significant and long-standing relief of pain syndrome [1, 2]. F. Barker et al. [3] analyzed 1195 cases and reported stable pain relief in 70% of cases and recurrences in 30% of patients. These data are similar to those confirming successful treatment of TN in 75% of cases. Possible complications are liquororrhea, infarctions and hematomas (up to 4% of cases), ipsilateral hearing loss (10%), aseptic meningitis (11%), impaired facial sensitivity (7%). Rare adverse event is in-jury of cranial nerves IV, V and VI [4, 5].

The common feature of percutaneous interventions (radiofrequency destruction, balloon compression, glycerol rhizotomy) is ablative mechanism. These procedures result TN dysfunction with various severity. At the same time, pain relief within 3 years may be achieved in 58—64% of patients after radiofrequency destruction [6, 7], in 53—54% — after glycerol blockade [8], in 69% — after balloon compression [9]. Weakness of the muscles of mastication as a complication of radiofrequency destruction is observed in 12% of cases, deafferentation pain — in 1.5% of cases [6, 7].

Gamma Knife (GK) as a surgical equipment occurred in the late 1990s. There are still no clear guidelines for stereotactic radiosurgery in patients with TN despite significant world experience in this surgery. It is necessary to clarify the indications for this approach in different types of TN, to assess the expected effectiveness and to determine the predictors of ineffective intervention.

The purpose of the study was to analyze the efficacy and safety of stereotactic radiosurgery (Leksell Gamma Knife) in patients with various types of TN, to compare the efficacy of this technique with other surgical methods.

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Material and methods

There were 156 radiosurgical interventions (Leksell Gamma Knife) at the International Institute for Biological Systems of St. Petersburg for the period from June 2009 to August 2016. The study enrolled 52 patients including 21 (40.4%) men and 31 (59.6%) women aged 31—79 years (mean age 58.2 and 60 years, respectively). Three patients underwent 2 courses of treatment with GK (in several months, 3 and 6 years after initial successful procedure). TN types were classified according to Burchiel’s classification for facial pain (2003). TN type 1 (typical) was diagnosed in 44 (84.6%) cases, TN type 2 (atypical) — in 4 (7.7%) patients, symptomatic — in 4 (7.7%) patients with multiple sclerosis. Left- and right-sided pain syndrome was observed in 22 (42.3%) and 30 (57.7%) patients, respectively. Time period between clinical manifestation and radiotherapy ranged from 1 to 40 years (median 8.5 months). The majority of patients appealed for medical care within 10 years after manifestation (Fig. 1).

One or several surgeries for TN were made in 19 (36.5%) patients: microvascular decompression of trigeminal nerve root (n=8), alcoholization of trigeminal branches (n=5), radiofrequency destruction of Gassarian ganglion (n=1), GK (n=3).

Pain syndrome severity was evaluated prior to surgery and in follow-up using pain scales and questionnaires. A visual analogue scale (VAS) (Huskisson et al., 1978) and Barrow Neurological Institute Pain Scale (BNIPS) (Riesenburger et al., 2009) were used.

Severity of neurovascular conflict was analyzed using the classification of Sindou et al. (2002). Doses of administered drugs, quality and duration of pain relief were considered. Complications were classified using the scale of Ibanez et al. (2011). Telephone interviewing was used to analyze follow-up data (mean follow-up 3 years, max 8 years). We considered pain syndrome severity in accordance with VAS, need for analgesics and doses of drugs, presence of postoperative complications. "Pain curves" were formed to clarify course of disease and clinical effectiveness of surgery (Figs. 7, 8). Recurrent TN was considered as aggravation of pain syndrome over VAS score 3 followed by increase of drug doses after primary postoperative favorable effect. Failed treatment was recognized in case of persistent stable postoperative pain in 12 months after surgery and later.

Treatment protocol

We used Leksell Gamma Knife 4C and Leksell Gamma Perfexion with planning station Gamma Plan (Elekta AB, Sweden). Leksell frame G stereotactic frame was fixed to the patient’s head under local anesthesia with Marcaini solution. After that, stereotactic MRI in T1, T2, CISS 3D modes was performed with or without contrast enhancement. CT was also applied for better visualization of the bones (in particular, passage of trigeminal nerve through the petrous part of the temporal bone). Anatomical target for radiotherapy was determined using integrated data of MRI and CT (trigeminal nerve root and adjacent neurovascular structures). Irradiation point was set within the trigeminal impression of the temporal bone behind the Gassarian ganglion (Fig. 2). The prescribed radiation dose was 90 Gy at 100% isodose.

Statistical analysis

Data are presented as mean/median [1, 3], 1st and 3rd quartiles. Non-parametric two-sided Mann—Whitney test and Fisher’s exact test were used to compare the groups. Time to delayed effect and disease-free period were estimated using Kaplan—Meier curves with 95% confidence interval.

Box-and-whiskers diagrams were used to illustrate the results. These plots consisted of median, interquartile range, max/min values within 1.5 of interquartile range and outliers. Calculations were performed using 3.4.3 — R software (survival package) [1].

Results

Mean preoperative VAS score of pain syndrome was 7.6. Even high doses of carbamazepine were ineffective in the majority of patients (BNIPS V, n=32, 61.5%).

According to preoperative imaging data, certain vessel as a potential cause of neurovascular conflict was not found in 11 (25%) patients. Vessel was adjacent to the trigeminal nerve root in 12 (27.3%) patients, tight contact of these structures followed by nerve dislocation was observed in 21 (47.7%) patients. Superior cerebellar artery resulted compression in 93.5% of cases, basilar artery — in 6.5% of cases.

Effectiveness of treatment for TN type 1

Reduced pain syndrome and decrease of the doses of drugs were observed in 38 (86.4%) patients. Mean time period to clinical effect ranged from several weeks to 12 months, as a rule. Mean time period to pain relief was 2.8/2 [1, 4] months, 95% CI — [2, 4] months (Fig. 3).

We did not find correlation of preoperative pain syndrome severity and duration of delayed effect (Fig. 4).

Surgery was ineffective in 6 (14%) patients with TN type 1 and persistent postoperative pain syndrome within 1 year after irradiation. In 8 (18%) patients, clinical improvement was followed by aggravation of pain syndrome that was regarded as a recurrence. Pain-free period in these patients ranged from 1 to 6 years. Mean time period to recurrence 2 years and 5 months (Fig. 5).

Follow-up period ranged from 6 months to 8 years (mean 3 years). Complete regression of pain and no need for medication (i.e., BNIPS I) were observed in 22 (50%) patients by the end of follow-up period. Seven (16%) patients had mild pain syndrome and did not require analgesics or small doses were effective (BNIPS II — III).
There was no correlation of GK effectiveness and age of patients (Fig. 6).

Local facial numbness after surgery was not associated with GK (Table 1).

Previous destructive surgery on trigeminal nerve was not a predictor of the effectiveness of radiosurgery in patients with TN type 1 (Table 2).

Higher grade of neurovascular conflict was observed in case of unfavorable outcome of treatment with GK and recurrent neuralgia (Table 3). However, these data should be interpreted with caution considering small sample size.

**Effectiveness of treatment for TN type 2**

Reduced pain syndrome after surgery was observed in 2 out of 4 patients with TN type 2. Recurrence occurred in 1 patient after 19 months.

Effectiveness of treatment in patients with multiple sclerosis

Regression of pain syndrome within a period from few days to 7 months occurred in 3 out of 4 patients with symptomatic TN. Recurrence was diagnosed in 2 cases.

**Complications after radiosurgery with GK**

The most common complications were facial numbness (grade 1a by the scale of Ibanez et al.) (n=28, 53.8%) and ipsilateral keratopathy (n=8, 15.3%). Trismus of the muscles of mastication developed in 2 (3.8%) patients. One patient noted hand numbness. There were no other neurological changes and complications.

**Case report No. 1**

A 79-year-old patient K. had suffered from shooting pain in the area of the second and the third branches of right trigeminal nerve within previous 15 years. She underwent right-sided microvascular decompression of trigeminal nerve root 4 years ago. Surgery resulted complete regression of pain syndrome (preoperative VAS score 10). However, recurrence occurred in 1 year after operation (Fig. 7). Over time, pain severity reached VAS score 8. The patient took Finlepsin 1600 mg daily without significant effect (BNIPS V). Radiosurgical treatment according with standard protocol was performed. Clinical improvement (complete regression) was noted in 3 months after irradiation. The patient stopped drugs intake. Recurrent pain VAS score 3 occurred 9 months later. Finlepsin 1 tablet per day was effective (BNIPS III). Facial numbness was absent.

**Case report No. 2**

A 53-year-old patient I. experienced shooting pain in the area of the first and the second branches of right tri-
geminal nerve within previous 9 years. There were no previous interventions for TN. Pain syndrome VAS score 8 was controlled by Finlepsin 800 mg/day (BNIPS IV) at admission. The patient noted a short-term aggravation of pain immediately after irradiation with subsequent gradual clinical improvement within 5 months. However, facial numbness developed.

Recurrent pain syndrome up to VAS score 6 occurred after 3 years of painless period. Five months later, the patient underwent redo irradiation (GK) and again noted early postoperative aggravation of pain followed by gradual improvement up to VAS score 4. The same pain persisted until the last survey in 3.5 years after treatment (Fig. 8).

Discussion

Mechanism of GK action

Exact mechanism of GK action on trigeminal nerve is still unclear despite a significant number of reports devoted to the effectiveness of GK for TN. GK does not result selective injury of any types of fibers [11, 12]. However, some authors reported higher sensitivity of gamma fibers of the trigeminal nerve [13].

Intact function of trigeminal nerve is observed in the majority of patients although tissue destruction effect of radiosurgery is supposed. So, many authors [14, 15] consider GK as not a destructive procedure. Currently, there are some assumptions about the mechanism of GK action. Few experimental studies have been conducted.

S. Lettmaier [14] consider that ionizing radiation has a different effect on abnormal and intact axons and affects only the axons responsible for ephaptic transmission. However, this version was refuted by G. Szeifert et al. [16]. They performed autopsy in a patient who died in 26 days after irradiation (dose 70 Gy). The cause of death was not associated with radiosurgical treatment. The researchers found a well-defined necrosis of proximal part of irradiated nerve without signs of viable fibers within the focus.

D. Kondziolka et al. [11] performed histological examination of trigeminal nerve root in two baboons in 6 months after irradiation with a dose of 80 and 100 Gy, respectively. Histological findings included local demyelination, axonal degeneration and necrosis in both models. However, spread of the lesion was greater in the specimen irradiated with a dose of 100 Gy. Z. Zhao et al. [17] reported similar data in a study with similar design involving 5 rhesus monkeys (focal demyelination, fragmentation and interruption of axons). Necrosis with intact axons around the lesion was detected in some areas. The effect depended on the dose of irradiation. M. Faraj et al. [18] studied the outcomes of irradiation with doses of 80 Gy and 89 Gy. The authors concluded that a dose of
Fig. 3. Time to clinical effect after GK irradiation in patients with TN type 1 (Kaplan—Meier curve).

Fig. 4. Delayed effect after GK irradiation for TN type 1.
89 Gy is the most acceptable to achieve analgesic effect in patients with TN.

**Effectiveness of GK**

Efficacy and safety of GK in the treatment of facial pain has been approved by multiple clinical trials [20—22] since introduction of this technique by L. Leksell [19]. According to trials with large samples, regression of facial pain may be achieved in 86—91% of patients. Moreover, pain relief usually occurs within a year after surgery [23—26]. However, J. Lucas et al. [25] reported recurrence in 45% of patients in 55.2 months after treatment. D. Kondziolka et al. [23] analyzed 503 patients. The authors reported adequate pain control (BNIPS I — III) in 80% of patients within 1 year, in 71% within 3 years, in 46% within 5 years and in 29% within 10 years after treatment. The best result (BNIPS I) was achieved in 29% of patients. These data are similar to those of other authors. For example, J. Régis et al. [26] analyzed 497 patients in long-term follow-up period. They reported that 64.9 and 33.9% of patients do not require drug therapy and haven’t pain after 5 and 14 years, respectively. However, only one third of patients have a persistent favorable effect despite relatively high delayed primary efficacy of treatment. Perhaps, this is due to unclear etiopathogenetic mechanisms of neuralgia and indications for GK.

A. Gorgulho [27] supposed that some inaccuracy of stereotactic technique with an error of 1.0—1.5 mm (target area 3 mm) results an unequal dose within root entry zone. This feature can potentially affect the outcome and causes recurrent TN [12]. However, some authors explain recurrent pain in different terms after treatment with GK by individual neuroplasticity of the brain.

There is a relatively high rate of recurrences (up to 61.5%) in case of symptomatic TN associated with multiple sclerosis [28—30]. GK demonstrates less favorable results compared with percutaneous interventions. Various authors [28—30] consider balloon compression as more preferable in these patients.

Few reports are devoted to application of GK in patients with postherpetic TN. In 2005, M. Keep et al. [31] suggested that irradiation of trigeminal nerve for acute paroxysmal pain and centromedian thalamic nucleus for burning sensation with a dose of 120—140 Gy is advisable for postherpetic TN. Treatment was carried out in 3 patients. Satisfactory regression of pain was noted in 2 patients. However, long-term follow-up was absent. The third patient was followed-up within 44 months. There was a reduced painful area with the same intensity [31]. D. Urgosik et al. [32] reported failed procedures with GK in 56% of cases.

**Predictors of successful treatment**

Various trials have been conducted in recent years. The main purposes of these studies are evaluation of effectiveness and analysis of the predictors of successful treatment (patients’ characteristics, type of pain, features of the procedure). The authors [23—26] are almost unanimous in their opinion that the highest effectiveness is observed in patients with TN type 1. J. Lucas et al. [25] analyzed 446 patients and found complete regression of
**Table 1.** Facial hypoesthesia after GK irradiation in patients with TN type 1

<table>
<thead>
<tr>
<th>Effect of GK</th>
<th>No numbness</th>
<th>Numbness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable effect, n (%)</td>
<td>13 (68)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Recurrence, n (%)</td>
<td>4 (21)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Unfavorable effect, n (%)</td>
<td>2 (11)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>In all</td>
<td>19</td>
<td>25</td>
</tr>
</tbody>
</table>

**Table 2.** Effectiveness of GK in patients with TN type 1 with and without previous destructive interventions

<table>
<thead>
<tr>
<th>Effect of GK</th>
<th>Previous intervention</th>
<th>No previous intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable effect, n (%)</td>
<td>20 (69)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Recurrence, n (%)</td>
<td>5 (17)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Unfavorable effect, n (%)</td>
<td>4 (14)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>In all</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 3.** Effectiveness of GK in patients with TN type 1 and various severity of neurovascular conflict

<table>
<thead>
<tr>
<th>Effect of GK</th>
<th>Grade 0 (no conflict)</th>
<th>Grade I</th>
<th>Grade II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable</td>
<td>—</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Recurrence</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Favorable</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Including</td>
<td>7</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>In all</td>
<td>11</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>

*Fig. 6. Correlation of GK efficacy and age of patients with TN type 1.*
pain (BNIPS I) in 62.9 and 22% of patients with TN type 1 after 1 and 5 years, respectively. In patients with TN type 2, these values were 47.5 and 9.2%, respectively [25]. K. Marshall et al. [24] reported significantly earlier recurrence in patients with TN type 2 in long-term period although Burchiel type of TN does not affect the primary outcome of the procedure. Recurrence-free period was 4.9 years in patients with TN type 1 and 1.7 years in those with TN type 2. Some researchers showed that patients with TN type 2 are more susceptible to pain recurrence after microvascular decompression [33] and irradiation with GK [34].

Another significant predictor of successful treatment with GK is facial numbness after irradiation [24, 25]. These data are similar to those of V. Pollock et al. [35] from the Mayo clinic. The authors analyzed patients after irradiation with doses of 70 and 90 Gy. Higher irradiation dose was associated with more common dysfunction of trigeminal nerve and regression of pain syndrome. A. Aubuchon et al. [36] also identified facial numbness as the most significant predictor of pain relief. At the same time, J. Régis et al. [26] did not observe this correlation.

Some authors [23—25] determine advanced age as a predictor of favorable result. J. Lucas et al. [25] reported that ceteris paribus probability of painless 5-year period is 10 and 45% in patients aged 40 and 80 years, respectively. Therefore, GK may be more preferable than microvascular decompression in advanced age patients regardless somatic state (or in case of contraindications for open surgery) considering above-mentioned data and minimal invasiveness of the procedure [37—39]. Some authors [23, 24, 26] determine any previous surgery for TN, radiofrequency destruction and micro-
vascular decompression as predictors of unsuccessful treatment with GK.

M. Zhang et al. [40] reported longer root of the trigeminal nerve as a predictor of more significant regression of pain syndrome.

Complications

Radiosurgery is characterized by small incidence of complications. One of the most common complications after treatment with GK is ipsilateral facial numbness. D. Kondziolka et al. [23] reported sensitive disorders in 11% of patients and deafferentation pain in 1 (0.19%) patient. The most severe complications were grade 1b by Ibanez et al. in our sample (need for drug therapy).

Conclusion

Application of GK in the treatment of TN and long-term outcomes after irradiation are analyzed in the article. All procedures were performed at the International Institute for Biological Systems of St. Petersburg. This sample is the largest in the Russian-language literature. In general, we observed high efficacy of GK in the treatment of patients with TN. These data are similar to literature data. However, we did not identify predictors of failed operation in our sample. We have shown that GK was effective for pain syndrome in the majority of patients with TN type 1. However, invasive interventions are characterized by higher efficacy than GK. The method was not very effective in patients with TN type 2 and multiple sclerosis followed by symptomatic TN.

The most important advantage of GK is non-invasiveness and low risk of complications. It is significant for advanced age patients with high surgical risk or severe concomitant diseases when open surgery is contraindicated.

It is necessary to inform patients about possible delayed effect prior to irradiation because delayed effect is observed in the majority of patients. Indications for GK irradiation should be determined considering pain severity, refractoriness to drug therapy and intensity of psychological experience of pain. Microvascular decompression is preferred for TN type 1 and 2 if immediate regression of pain is required and imaging methods confirm significant vascular compression of trigeminal root. At the same time, patient’s decision is essential in case of choice between GK and microvascular decompression for TN type 1 and 2. It is important to inform the patient not only about possible postoperative complications, but also about the likelihood of subsequent recurrence.

Authors declare no conflict of interests.

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Commentary

Trigeminal neuralgia (TN) is a syndrome characterized by paroxysmal acute, burning pain in the area of trigeminal nerve innervation. Pain results reduced quality of life and depression up to suicidal thoughts. Currently, the “gold standard” of surgical treatment for TN is microvascular decompression aimed at elimination of neurovascular conflict. Microvascular decompression is followed fast, significant and long-standing regression of pain in 70% of cases and over with small number of complications. Keypoint is to identify the root of the problem - vessel compressing the trigeminal nerve. If a compression is identified, there is no discussion. The authors reported the most significant experience of GK irradiation for TN in the Russian-language literature. All procedures were made at the International Institute for Biological Systems of St. Petersburg. In general, the authors confirmed well-known data about effectiveness of radiosurgery for TN. However, analgesic effect is less than after microvascular decompression. Long-term regression of pain may be associated with facial numbness. The most important advantage of radiosurgery, in particular GK, is minimal invasiveness and low risk of complications. The authors use adequate assessment of pain syndrome severity and comprehensively describe features of treatment. Delayed effect after irradiation is emphasized, that is disadvantage of this method compared with invasive interventions. It is worth to note temporary regression of pain syndrome. Recurrent pain syndrome occurred in 15% of patients after previous clinical improvement. It is rightly emphasized that stereotactic radiosurgery is advisable in advanced age patients with high surgical risk or severe concomitant diseases and contraindications for open surgery.

Mean follow-up was 3 years. The study included 52 out of 156 patients who underwent treatment. Unfortunately, the authors did not describe features of sampling. The authors argue that patient’s decision is crucial in choice of GK or microvascular decompression for TN type 1. It is important to inform a patient not only about possible postoperative complications, but also about delayed effect and recurrence rate. According to preoperative imaging, certain vessel as a potential cause of neurovascular conflict was not found only in 11 (25%) patients, vessel adjoined to trigeminal root in 12 (27.3%) patients. Close contact followed by root displacement was observed in 21 (47.7%) patients. So, there is a question. Perhaps, microvascular decompression as a preferable method with higher efficiency and minimal incidence of complications should be more aggressively offered in patients with neurovascular contact, shouldn’t it? Additional argument in favor of this statement is occurrence of post-irradiation complications (facial numbness and even ipsilateral keratopathy) in more than half of patients.

Microvascular decompression is still preferred for TN type 1 and 2 if immediate regression of pain syndrome is required and preoperative imaging confirms compression and dislocation of trigeminal root. Radiosurgery may be considered as a preferable intervention in advanced age patients or in those with contraindications for open surgery.

A.V. Golanov (Moscow, Russia)
Chronic pelvic pain (CPP) is a chronic or persistent pain in men and women. According to the etiology, CPP may be divided into diseases with a known cause (infection, cancer, etc.) and those without obvious reasons. The second group is determined as “chronic pelvic pain syndrome” [1, 2].

According to the International Association for the Study of Pain, prevalence of CPP is 6—7% [3, 4]. Women with complaints of CPP account for about 15—20% of all patients of gynecological consultations and up to 10% of all women visiting general practitioners.

Pathophysiological mechanisms of CPP are still unclear. According to modern concepts, CPP is a dysfunctional pain syndrome involving nociceptive, inflammatory, neuropathic and psychogenic aspects. From a clinical point of view, CPP is considered as a complex of various syndromes, which are combined into clinical and pathophysiologic domains in accordance with main causes and levels of damage [1, 5—12]. Etiology of pain syndrome remains unknown in almost 30% of cases [1, 2]. Even treatment of certain disease (endometriosis, interstitial cystitis) does not always result analgesic effect, and persistent pain syndrome requires special methods and approaches. First of all, these measures should be aimed at correction of the main mechanism involved in the development of pain.

Pharmacotherapy is used as a first-line treatment. Anticonvulsants and antidepressants are advisable in some patients with clinical signs of neuropathic pain (alodynia, hyperalgesia, hyperpathy), muscle relaxants or local injections of botulinum toxin — in patients with myofascial pain syndromes of pelvic muscles. Nevertheless, even adequate therapy is associated with gradual impairment of clinical effect or initially low efficacy in some patients [13—16].

Study of this problem is relevant due to advanced number of patients and low efficiency of treatment of persistent pain syndrome. Neurmodulation has been recently used for chronic pain syndromes including CPP in case of ineffective medication. However, trials devoted to the use of these methods for CPP include small samples and have insufficient methodological and evidence base [17—38]. The use of neurmodulation for CPP is historically closely associated with the use of SNRS in...
patients with pelvic organ dysfunction. W. Brindley performed the first electrostimulation of the bladder in 1976 in a patient with multiple sclerosis followed by urinary incontinence. Stimulation resulted prolonged “dry intervals”. Subsequent studies showed that stimulation results reduced tone of external urethral sphincter and perineal muscles and reflex contraction of detrusor in patients with impaired evacuation function. In patients with impaired reservoir function, this approach results contraction of external urethral sphincter and suppression of afferent impulses to towards urination center.

Mechanism of neuromodulation in patients with CPP is still unclear [18, 39—42]. However, there is evidence of its effectiveness for pelvic organ dysfunction (POD) [17—26]. Interstim neurostimulation system (Medtronic, USA) was officially approved in the USA for urinary incontinence in 1998. This allowed the use of SNRS for the treatment of various problems associated with POD [27]. Since 2014, the European Association of Urology recommends the use of neuromodulation for CPP [26].

Material and methods

The study included 32 patients with CPP (26 (81.25%) women, 6 (18.75%) men) aged 21—79 years (median 51 years). Mean preoperative duration of pain was 8.22±5.33 years (range 1—31 years). Mean VAS score of pain was 8.61±0.91 (range 6—10). Thirteenth (40.6%) patients took narcotic analgesics before surgical treatment. Morphological substrate of pain was diagnosed in 17 (53.125%) patients: endometriosis (n=8), adnexitis (n=2), interstitial cystitis (n=6). One patient had benign prostatic hyperplasia. Morphological substrate was not identified in 15 (46.875%) cases and syndromic diagnosis was established.

Patients were referred to the Burdenko Neurosurgery Center with confirmed diagnosis of CPP after comprehensive multidisciplinary and multimodal examination. Pain syndrome was evaluated using international quantitative scales: DN4, Pain Detect, LANSS [43]. Severity of pain syndrome was assessed using VAS, psychological status — using Hospital Anxiety and Depression Scale (HADS) [45]. Quality of life was studied using the modified Pain Quality of Life Card questionnaire (PQLS) [43, 44].

We analyzed effective parameters of stimulation using patient’s diary and programming protocol. Effectiveness of treatment was assessed in 6 and 12 months after implantation of permanent neurostimulation system and then annually by in-person consultation.

X-ray examination of the pelvis in frontal and lateral projections was performed to control position of electrode and optimize stimulation programs. 3D-CT of pelvic bones was additionally performed if it was necessary.

Effectiveness of stimulation was determined as excellent in case of reduction of pain severity by 70% and over, good — by 50—70%, satisfactory — by 30—50% and unsatisfactory — by less than 30%.

Surgery consisted of 3 stages in all cases.
1. **Implantation of test electrode.** In most cases, it was performed by puncture under local anesthesia. The implantation technique differed depending on the type of neuromodulation (sacral, pudendal, epidural, stimulation of peripheral field).
2. **Test period.** The most suitable parameters of stimulation were determined using an external test stimulator within 7—14 days. Test period was considered positive if pain severity was reduced by 50% and over.
3. **Implantation of neurostimulation system in patients with positive test period.** The implanted electrode was passed through the subcutaneous tunnel towards the

*Fig. 1. X-ray scan.*
Anatomical landmarks for defining the S3 hole (explanations in the text).
place of generator implantation. Generator was implanted under the skin of buttock or iliac area.

Test neurostimulation of sacral roots was used in 15 cases (unilateral in 8 cases, bilateral in 7 cases). In 3 patients, electrode was deployed within lumbar enlargement of spinal cord. Combined neurostimulation was used in 14 patients: SNRS + PNS in 3 patients, SNRS + PNFS — in 4 patients, SCS + SNRS — in 5 patients, SCS + PNFS — in 2 patients. Pain severity was assessed in all patients using VAS scoring system.

Sacral stimulation (SNRS). In most cases, sacral electrode was implanted into the third sacral orifice using standard transforaminal procedure. This orifice is located at the intersection of vertical line through medial edges of sacral orifices and horizontal line along inferior edge of sacroiliac joint (Fig. 1). Fluoroscopy in two projections and intraoperative electrostimulation were used to control position of electrode [46]. Signs of ideal position of the electrode in direct projection — from the inside outwards, in lateral projection — inwards backwards. Stimulation should result contractions of the anal sphincter and/or dorsal flexion of the ipsilateral big toe. However, the main result is maximum coverage of pain area with paresthesia.

Four patients underwent anterograde implantation of electrodes through hiatus sacralis [47, 48]. This orifice is determined by palpation. Then, Tuohy needle is inserted almost perpendicularly to the skin until loss of re-
sistance is sensed. Finally, the tip of the needle is inserted deeper by 1—1.5 mm under fluoroscopic control. Next, an electrode is implanted through the needle under stimulation control up to maximum coverage of painful area with paresthesia. This approach is able to cover almost any painful pelvic area using a single puncture. It is rarely used due to advanced risk of infectious complications (proximity to the anus). Moreover, thin skin in this area does not always allow reliable fixation of the electrode.

Similar to traditional implantation through the lateral sacral orifices, fluoroscopy in two projections and intraoperative electrical stimulation were used to control position of the electrodes during anterograde (transhiatal) implantation (Fig. 2).

Pudendal nerve stimulation. There are several basic techniques for implanting electrodes into the area of pudendal nerve. We used so-called STAR-technique of K. Heinze et al. [49, 50] (according to initial letters of the names of anatomical structures: Spine (sciatic spine), Tuberosity (sciatic tuber), Acetabulum (center of the acetabulum), Rim (anal sphincter)). Electrode implantation using this method is shown in Fig. 3. Horizontal and vertical lines are drawn through the points A and T. Their intersection corresponds to sciatic spine (point S). A line is drawn from the point S towards anal sphincter (point R). A line drawn through points T and R is divided in half. Middle point of this line determined the first puncture (yellow circle). The tip of the triangle (point S) is target for needle movement and anatomically corresponds to pudendal nerve trunk (red circle). A patient is in prone position with rollers under pelvic bones and ankle. Electrode’s position is controlled by intraoperative stimulation, which should result paresthesia within painful area and/or contraction of the anal sphincter.

Epidural spinal cord stimulation. Implantation of an electrode for spinal stimulation was carried out according to standard procedure in patient’s prone position. Epidural puncture was carried out using Tuohy needle through paramedian approach under 30° to spinous process and 15° to midline at the level of LIII — LIV. Electrode’s position is controlled by intraoperative stimulation to achieve paresthesia within painful zone. Therefore, the position could vary from inferior parts of lumbar enlargement to conus medullaris (ThXI — LII) (Fig. 4).

Fig. 4. Spinal cord stimulation.
The electrode is epidurally deployed at the level of ThX — ThXII.

Fig. 5. Example of combined stimulation.
One electrode is installed in sacral canal, the other — subcutaneously within innervation area of the left iliac-inguinal nerve.
Peripheral nerve field stimulation. In case of this technique, electrode was directly implanted into painful area. The method implies subcutaneous location of stimulating electrode within functional area of the nerves innervating skin of the pelvic region (ilioinguinal, iliohypogastric, pudendal, femoro-pudendal, etc.). Peripheral nerve field stimulation is suitable for small painful areas (length up to 7—10 cm and width up to 2 cm). Cross-stimulation may be applied if painful area exceeds standard dimensions for PNFS. This method implies deployment of cathodes on subcutaneous electrode and anodes on sacral (or spinal) electrode (Fig. 5). Paresthetic (i.e. analgesic) area is significantly enlarged in this case.

We were guided by localization of pain during implantation of the electrodes. So, unilateral radicular electrostimulation was preferred for unilateral local pain. Isolated stimulation of pudendal nerve was performed for pain within innervation zone of this nerve. Spinal cord stimulation was made in case of extended painful areas, in particular thighs, buttocks or lower lumbar regions. Combined stimulation methods were used in case of insufficient coverage of painful area after implantation of a single test electrode and in extended painful areas.

Selection of stimulation programs was also determined by intention to cover all painful area with paresthesia. Amperage was 1.0—15.0 mA, pulse width — 60—450 μs, frequency — 2—250 Hz. The most common values of frequency were 60, 90, 110 Hz, pulse width — 210, 240 μs, amperage — 2.0—7.0 mA. Low-frequency stimulation (15—30 Hz) or its combination with high-frequency mode followed by within-day alternation was preferred for concomitant pelvic organ dysfunction.

Five patients with implanted unilateral sacral electrode required implantation of the second contralateral electrode for complete coverage of painful area despite effective test period. For the same reason, 2 patients with unilateral sacral electrode underwent additional implantation of the second electrode after 1 year (on S3 from the opposite side and epidural implantation at the level of ThX — ThXI). Epidural implantation of an electrode at the level of Th10—Th11 was made after 1 year in one patient with bilateral sacral stimulation.

Results

Test period did not result significant decrease of pain syndrome (by 50% of VAS score) in 5 (15.62%) patients. In these cases, test electrodes were removed and patients continued conservative treatment. Test period was considered as positive in 27 (84.37%) patients. Systems for permanent neurostimulation were installed in these patients.

Mean preoperative VAS score of pain syndrome was 8.61±0.91 in patients with permanent electrostimulation. Mean VAS score decreased up to 3.53±1.20 in 12 months after surgery. Excellent effect (decrease of VAS score by 70% and over) was achieved in 28.15% of pa-
tients, good (by 50—70%) — in 50%, satisfactory (by 30—50%) — in 15.6% of patients.

The majority of patients had a long history of pain in our sample. Some authors reported inverse correlation of pain duration and effectiveness of neurostimulation [51]. On the one hand, this phenomenon is associated with central sensitization and permanent neuronal hyper-excitability, on the other hand — with appearance of so-called painful behavior and anxiety-depressive disorders. However, we did not find this correlation in our sample despite long-term history of pain (Fig. 6).

In our study, 40.6% of patients took narcotic analgesics prior to surgery. All patients were able to completely abandon drugs in 1 year after stimulation onset. Anxiety and depressive disorders were assessed using the HADS scale. Mean preoperative depression score was 5.00±1.81, in follow-up — 4.25±1.37 (p<0.05). Mean preoperative anxiety score was 12.93±3.53, in follow-up — 7.75±1.19 (p<0.05). Permanent neurostimulation resulted reduced anxiety and depression that can indicate secondary nature of anxiety and depressive disorders.

According to PQLS scale, neurostimulation results improvement of quality of life in many aspects. Thus, mean score of the strongest background pain (PQLS scale) prior to stimulation was 8.59±1.16, in 1 year after stimulation onset — 5.44±1.60 (p<0.05). The strongest pain’s assault score before stimulation was 9.34±0.60, in 1 year after stimulation onset — 6.81±1.33 (p<0.05) (hereinafter, values are given as scores before neurostimulation and in one year after surgery, respectively). Intensity of the weakest background pain was 6.28±1.88 and 3.4±1.24 (p<0.05). Intensity of the weakest pain’s assault was 6.56±1.74 and 3.77±1.67 (p<0.05). Incidence of pain attacks was 9.18±1.14 and 5.33±2.21 (p<0.05). Mean intensity of background pain was 7.31±1.33 and 4.25±1.37 (p<0.05). Mean intensity of pain’s assault was 7.75±1.19 and 4.77±2.08 (p<0.05). Need for medicines was 12.93±2.27 and 7.77±2.70 (p<0.05). Influence of pain on well-being was 8.56±2.46 and 5.88±2.51 (p<0.05). Effect of pain on mood was 9.34±1.35 and 6.03±2.10 (p<0.05). Influence of pain on daily physical activity was 8.21±1.53 and 4.55±1.90 (p<0.05). Effect of pain on passive rest was 7.65±1.55 and 5.18±1.61 (p<0.05). Influence of pain on self-care was 5.78±2.23 and 2.77±1.57 (p<0.05). Influence of pain on relationships with other people was 7.03±2.20 and 5.14±1.81 (p<0.05). Effect of pain on sleep was 7.15±1.98 and 5.00±1.81 (p<0.05). Influence of pain on sexual activity was 9.78±0.90 and 6.96±2.00 (p<0.05).

Thus, permanent electrostimulation affected all variables of PQLS scoring system of quality of life. The most significant findings were reduced background pain, number of attacks, need for medicines, increased daily motor activity, social intercourse, self-care ability, improvement of sleep and sexual activity.

There were no infectious and neurological complications. Technical complications associated with migration of the electrode were identified in 5 patients. In all cases, these were patients with implanted system for sacral stimulation. Electrode migration was manifested by displacement of paraesthesia zone and reduced effect of stimulation. Complication was diagnosed using X-ray examination. In all cases, surgical correction of electrode position was performed with restoration of effective neurostimulation.

**Discussion**

Various authors reported effectiveness of neuromodulation for chronic pain syndromes [52—54]. Spinal cord stimulation has been used for more than 40 years for various pain syndromes [52]. In 1997, K. Kumar et al. [53] reported that this method entered the top five effective approaches for peripheral neuropathy and complex regional pain syndrome. Currently, researches of the effectiveness of neuromodulation for pain syndromes are being continued and CPP is one of the main directions of these trials [41, 52].

In 2015, K. Peters et al. [18] reported the use of sacral electrostimulation in 7 patients with interstitial cystitis/painful bladder syndrome. There was almost 2-fold decrease of pain syndrome after 24 weeks of follow-up (49%, VAS score decrease from 7.9 to 4.0). M. Lavonius et al. (2017) [54] analyzed effectiveness of sacral electrostimulation in 4 patients with endometriosis. Surgical removal of endometriotic foci did not decrease intensity of pain and dysuric disorders in those women. Follow-up period was 2.5 years. All patients noted reduced pain syndrome, improvement of dysuric disorders and quality of life. P. Sokal et al. [55] reported 9 patients with pharmacoresistant pelvic pain. Neurostimulation resulted significant analgesic effect after 6 months (preoperative VAS score 9, after 6 months — 2). However, aggravation of clinical effect up to 6 scores was observed a year later. K. Peters [56] consider that pudendal nerve stimulation should be used as an alternative approach in patients with ineffective sacral electrostimulation. S. Siegel et al. [57] used sacral stimulation in 10 patients with pelvic pain. The electrodes were placed in the holes of S3 and S4 in 8 and 2 cases, respectively. Stimulation was followed by decrease of VAS score from 9.7 to 4.4 in 9 out of 10 patients.

Six patients reported a significant improvement of pain within 19 months on the average. S. Abdel-Aziz [58] noted 50% decrease of pain syndrome and improvement of daily activity in 5 patients after combined spinal and sacral stimulation. The authors recommended combined neurostimulation for patients with CPP.

We used various neurostimulation techniques: permanent stimulation of sacral roots, permanent stimulation of pudendal nerve, spinal cord stimulation, peripheral field stimulation and their combinations. The choice
of certain stimulation mode depended on localization of pain and its correspondence to the innervation area of chosen nerve. Additional electrode was implanted in case of incomplete coverage of pain area by a single electrode.

In our sample, neurostimulation resulted a good analgesic effect (over 50%) in most patients (78.15%). The cause of CPP was defined in 17 patients and unclear in 15 patients. However, this did not affect the effectiveness of neurostimulation. According to some authors, duration of pain syndrome is one of the predictors of the effectiveness of stimulation in patients with chronic pain. However, we did not observe this correlation in our sample. All patients took narcotic analgesics before neurostimulation. The need for medication was absent in 1 year after stimulation onset.

The most significant outcomes associated with improved quality of life were reduced background pain, number of attacks, improvement of daily physical activity, ability to self-care, social intercourse, sleep and sexual activity, reduced intake of the drugs.

Some authors reported the effect of anxiety-depressive disorders and social factors on the effectiveness of permanent stimulation. In particular, N. Khan et al. [59] found impaired clinical effect, aggravation of pain syndrome and advanced disability in patients paying bank loan, taking opioids and in those with disabilities. Psychogenic component was verified in all patients of our sample. It should be noted that patients with a stable analgesic effect had reduced anxiety and depression. We assume secondary nature of anxiety and depressive disorders in this case.

Patients with a negative test period had high rates of anxiety and depression by the HADS scale. So, predominant psychogenic component may be supposed. In this regard, we believe that psychotherapist’s consultation is necessary prior to surgery to exclude primary mental disorders.

Conclusion

Thus, we showed that neuromodulation is followed by reduced pain syndrome by more than 50% in most patients with CPP. We assume that outcomes do not depend on etiology and duration of pelvic pain. A combination of techniques is often required to obtain favorable results. Implementation of neurostimulation systems is minimally invasive procedure.

Despite initial success of the use of surgical neuromodulation for CPP, further analysis of this method, clarification of indications and contraindications and development of uniform selection criteria for surgery are required. Another aspects are time for neurostimulation onset and prevention of possible complications.

Authors’ participation:

Concept and design of the study — O.K.
Collection and analysis of data — A.A.
Statistical analysis, writing the text — A.K.
Editing — V.L.

Authors declare no conflict of interests.

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The article is devoted to the use of neurostimulation in patients with chronic pelvic pain (CPP). Burdenko Neurosurgery Center has the greatest experience in the country regarding neuromodulation for complex pain syndromes. CPP syndrome is difficult for treatment due to unclear etiology and pathogenesis. Therefore, all trials and reports devoted to this issue are extremely relevant. The authors reported surgical outcomes in 32 patients with CPP. Systems for permanent stimulation were implanted in 27 cases after positive test period. Much attention is paid to individual approach to each patient and choice of optimal surgical strategy. A total of 5 different stimulation methods were described, which were used individually or in combination depending on features and localization of pain. Pain syndrome, psychological status and effect of pain on the quality of life were assessed using international rating scales and questionnaires before and after surgery. The authors obtained good results regarding decrease of pain syndrome (as a result, refusal narcotic analgesics), anxiety and depression and improvement of overall quality of life in these patients.

However, there are some questions to this report about methodological aspects of the research. It would be desirable to indicate time period (years) for collected data. Test period also needs to be clarified. Did only the degree of pain reduction affect the result of test? Were any predictors of negative result (other than psychogenic component) identified? How were the permanent systems implanted? Were the same electrodes used as in the test period? Did the authors notice any effect of stimulation on pelvic organs functions or other side effects of stimulation? It is interesting to know the authors’ opinion about decrease of the effectiveness of stimulation over time. Was there this tendency? It is important to know exactly which systems and electrodes were used for surgical treatment. Such variable as “incidence of painful attacks” is described in the “Results”. What was the period of time for the frequency estimated (day, month)? The authors reported so variable as “need for medicines”. However, assessment and measure of this parameter were not described.

Despite some questions, the article is undoubtedly of great practical and scientific interest and the research should be continued.

D.A. Rzayev (Novosibirsk, Russia)
Increased incidence of benign and malignant tumors including brain tumors is observed in recent decades. Annually incidence of primary CNS tumors in young patients is 10.94 cases per 100,000. Over 50% of brain tumors are benign in patients of reproductive (15—39 years) age. These are pituitary tumors (29%), meningiomas (14%) and neuromas (9%), etc. Gliomas account 1/3 of all brain tumors, while 74% of them are malignant [1].

Survival rate in patients with benign and malignant brain tumors is increasing due to improved neurosurgical techniques, the use of modern modes of chemotherapy and radiotherapy. Five-year survival after diagnosis of benign CNS tumor is 90%. In patients with malignant CNS tumors this value is 74% for patients aged 0—19 years and 62% for patients aged 20—44 years [1].

It is known that neurosurgery for brain tumors (especially in hypothalamic-pituitary area), chemotherapy and radiotherapy for malignant brain tumors of any localization may be complicated by hypogonadism and infertility. At present, a simple and reliable method of preserving male fertility is sperm cryopreservation. Neurosurgeons as well as oncologists and radiologists should inform patients with brain tumors about a potential risk of hypogonadism and infertility after treatment and about opportunities of sperm cryopreservation, which increases the chances of having future genetic progeny.

Keywords: hypogonadism, male infertility, brain tumors, hypothalamo-pituitary tumors, spermatozoa cryopreservation.
Impaired secretion of gonadolibersins and/or gonadotropins and secondary hypogonadism. These tumors are usually hormone-producing and inactive pituitary adenomas, craniopharyngiomas, etc. Clinical symptoms of hypogonadism are impaired sexual function (decreased libido, erectile dysfunction) and spermatogenesis (infertility). Long-term androgen deficiency also results osteoporosis, metabolic and cardiovascular disorders.

Prevalence of hypogonadism in patients with pituitary adenoma is over 60% [9—11]. Adenoma results compression of pituitary gland and impairment of its gonadotropic function. Excessive hormonal secretion followed by reduced level of testosteron and impaired spermatogenesis is another negative result of hormone-producing tumors besides mass effect. As a rule, these tumors release prolactin (prolactinoma) and ACTH (corticotropinoma followed by clinical signs of Cushing disease). Growth hormone-secreting adenomas are rarer (somatotropinoma followed by clinical symptoms of acromegaly). Endocrine-inactive pituitary adenomas are not accompanied by clinical symptoms of hormonal hypersecretion. These neoplasms are characterized by slow growth and result pituitary gland dysfunction (hypopituitarism). The most common primary symptoms of disease are decreased libido and erectile dysfunction. However, patients with these disorders rarely appeal to the doctor. As a result, these tumors remain undiagnosed for a long time until appearance of visual and neurological disorders caused by mass effect of the tumor. Long-term compression of pituitary gland may be followed by atrophy of gonadotropin-secreting cells and persistent hypogonadism.

Hyperprolactinemia is caused by prolactinoma in most cases. It is one of the leading causes of male infertility [12]. Therapy with dopamine agonists is highly effective for prolactinoma and results reduced dimensions or regression of the tumor in 80—85% of patients, significant decrease or normalization of the level of prolactin in 70—80% of cases and recovery of gonadotropic function in 80% of patients. However, persistent hypogonadism caused by atrophy of gonadotropin-secreting pituitary cells is observed in 20% of men with prolactinoma and normoprolactinemia [13]. Asthenoteratozoospermia is characteristic for pituitary adenoma violation of spermatogenesis [3].

Neurosurgery for pituitary adenoma can also result occurrence or aggravation of hypogonadism due to intratumoral pressure. Radiotherapy is used in patients with pituitary adenoma after non-radical neurosurgery. Secondary hypogonadism is diagnosed in 80—90% of cases due to radiotherapy-induced injury of pituitary tissue [14].

The most common endocrine disorders, primarily hypogonadism, are observed in patients with craniopharyngiomas (disembrigenetic hypothalamic-pituitary benign tumors). It is known that these tumors are accompanied by hypogonadism in 60% of cases prior to surgery. Incidence of this complication is increased up to 80—100% after excision of these tumors regardless localization and surgical approach [15, 16].

High incidence of hypogonadism in men with hypothalamic-pituitary tumors is accompanied by significantly reduced quality of life, sexual and reproductive potential.

It is necessary to examine androgenic status (LH, FSH, testosterone) in all men with hypothalamic-pituitary tumors prior to surgery. Moreover, sperm quality assessment is advisable in those interested for preserved fertility. However, these studies are not preoperatively carried out in neurosurgical clinics as a rule.

Testosterone replacement therapy is currently preferred for secondary hypogonadism. Medication eliminates androgen deficiency, normalizes sexual function and significantly improves quality of life. However, these drugs do not affect recovery of reproductive function.

There are no clear literature data regarding feasibility of sperm cryopreservation in patients with benign hypothalamic-pituitary tumors. Indeed, on the one hand, hypogonadism and impaired sperm quality have been already diagnosed at the stage of tumor diagnosis as a rule. On the other hand, stimulating monotherapy with chorionic gonadotropin or combined therapy with follicle-stimulating hormone drugs are possible if reproductive rehabilitation is required. These approaches improve sperm quality and increase the likelihood of pregnancy in a female partner in some cases [17]. Currently, there are no randomized trials devoted to the effectiveness of this therapy in patients with hypothalamic-pituitary tumors. Moreover, therapy is associated with certain risk of tumor progression prior to surgery and after non-radical operation. An important factor is high cost of the treatment.

Gonadotropin therapy is justified in patients after radical excision of tumor. Courses up to 3—6 months are advisable under MRI control of the brain. Sperm cryopreservation is advisable in patients with secondary hypogonadism who are interested for reproductive potential. This procedure should be performed after gonadotropin therapy followed by restoration of sperm quality. Continued testosterone therapy is recommended after induction of pregnancy or sperm cryopreservation.

It is reasonable to preoperatively inform patients with intact gonadotropic function about the risk of various endocrine disorders (including hypogonadism) and potential advisability of preoperative sperm cryopreservation. This strategy should be applied primarily in young men, as well as in all patients who any interested for reproductive potential.

Reproductive disorders in patients with brain malignancies. Malignant tumors may be localized in hypothalamic-pituitary zone (germ cell tumors, malignant gliomas, metastases, etc.) or in other areas without involvement of endocrine structures. However, combined treatment including surgery, chemo- and radiotherapy often results various endocrine disorders including hypogo-
naddism and infertility regardless localization of tumor. S. Shalitin et al. [18] reported various endocrine disorders in 57% of patients who underwent treatment for brain tumors. At the same time, complications of antitumor therapy can develop during treatment, immediately after therapy and in long-term period.

Cranial irradiation can cause pituitary gland injury with the loss of all pituitary functions (including gonadotropic). Incidence of radiotherapy-induced secondary hypogonadism in patients with brain tumors is 5—61% depending on the dose and mode of irradiation. Standard scheme of irradiation in patients with brain tumors implies overall dose of 30—50 Gy. The most significant risk factor of hypogonadism is the dose of cranial irradiation over 30—40 Gy [19]. Thus, clinically significant secondary hypogonadism occurs in 20—50% of patients exposed to a dose of more than 30—40 Gy [20]. Cranial and spinal irradiation is used in some treatment modes for brain tumors and can result primary lesion of gonads [21].

Chemotherapy has a direct gonadotoxic effect. Alkylating drugs are the most toxic for male fertility because these medicines damage spermatogenic epithelium. Therefore, sperm sampling should be carried out before radio- and/or chemotherapy onset, since sperm quality is significantly impaired during the treatment. Testicular tissue cryopreservation is being developed for boys in prepubertal age [22—24].

Case report No. 1

A 30-year-old patient K. noted headache 6 months ago. Deterioration of visual function occurred within the last 3 months that required survey. MRI of the brain revealed giant multinodular endosuprasellar pituitary adenoma. The patient is married and has not children. Impairment of libido and erectile dysfunction are not noted.

Examination at the Neurosurgery Center: chiasmatic syndrome (bitemporal violation of visual acuity and visual fields), no hormonal disorders, prolactin 430 mU/l (155—974), LH 0.2 mU/l (1.5—9.3), testosterone 1,1 nmol/l (12—35). The patient was informed about the high risk of hypopituitary disorders/hypogonadism after surgery and the possibility of sperm cryopreservation. Patient turned to a cryobank prior to surgery for analysis of spermogram. Examination found no abnormalities, and spermatozoa were cryopreserved.

The patient underwent subtotal endonasal transphenoidal endoscopic removal of endocrine-inactive pituitary adenoma on January, 30, 2015. Recovery of visual function was observed after surgery. However, postoperative panhypopituitarism (secondary hypothyroidism, hypocorticism, and hypogonadism) and diabetes insipidus required therapy with hydrocortisone, levothyroxine and desmopressin. A control MRI 6 months later revealed a large residual tumor within the cavernous sinus.

In August — September 2015, a course of stereotactic radiotherapy was performed for residual tumor (Novalis linear accelerator with a photon energy of 6 MeV). There were 30 fractions by 1.8 Gy up to overall dose of 53.7 Gy.

Control examination in 6, 12 and 24 months after surgery confirmed persistent panhypopituitarism and diabetes insipidus. Hormonal blood test (12 months after surgery): FSH 0.8 mU/l (1.55—9.74), LH 0.2 mU/l (1.5—9.3), testosterone 2.1 nmol/l (12—35). Spermogram: 5 million spermatozoa in 1 ml of ejaculate (WHO norm ≥15 million/ml), normal forms — 0% (WHO norm according to Kruger’s criteria ≥4%), progressive motile A + B — 0% (WHO norm ≥32%). Asthenoteratozoospermia was confirmed.

Gonadotropin therapy was not prescribed considering possible stimulating effect on residual tumor. Testosterone replacement therapy was prescribed (testosterone undecanoate). Treatment of infertility using ART and cryopreserved sperm in 2.5 years after surgery resulted birth of a healthy child.

Case report No. 2

In October 2013, a 21-year-old patient S. noted headache, periodic dizziness, nausea and vomiting. Contrast-enhanced MRI of the brain revealed a pineal tumor with initial signs of occlusive hydrocephalus. He was hospitalized for an open biopsy. The result of a biopsy is a germinoma. The patient was informed about the risks of treatment and potential impairment of fertility. However, the patient refused cryopreservation. Treatment was initiated according to the protocol for germinoma. There were 4 courses of chemotherapy (cisplatin + etoposide) followed by radiotherapy with irradiation of the entire ventricular system (overall dose of 24 Gy). Spermogram was analyzed in 3.5 years after the treatment. There was a significantly reduced number of spermatozoa up to 7 million per 1 ml of ejaculate (WHO norm ≥15 million/ml), progressive motile (A + B) — 36% (WHO ≥32%), immotile 50% (WHO norm <30%), normal forms — 1% (Krugers’s strict criteria >4%). So, asthenoteratozoospermia was confirmed. Hormonal blood test: FSH 9.9 mU/l (1.4—18.1), LH 5.92 mU/l (1.5—9.3), testosterone 9.52 nmol/l (12—35), inhibin B 78 pg/ml (120—470). Prospects for restoration of reproductive function are clearly reduced in a patient considering significant deterioration of sperm quality after chemoradiotherapy.

Case report No. 3

A 28-year-old patient S. has noted headache and rare difficulties in words pronouncing since October 2014. MRI of the brain on September 5th, 2015 revealed a small tumor in the left frontal lobe without contrast uptake. Tumor was removed on November 30th, 2015 (anaplastic astrocytoma, WHO Grade III). Chemoradiotherapy was applied considering tumor morphology. Patient was informed about the risk of infertility and the possibility of sperm cryopreservation be-
fore the treatment. Patient turned to a cryobank prior to surgery for analysis of spermogram. Examination found no abnormalities, and spermatozoa were cryopreserved.

In February — April 2016, a course of stereotactic radiotherapy was performed (Primus linear accelerator with a photon energy of 6 MeV). There were 30 fractions by 2.1 Gy at the isocenter up to overall dose of 63 Gy. Subsequent 6 courses of chemotherapy included lomustine + vincristine + natulan. The last course was conducted in December 2016. All three chemotherapeutic agents have a negative effect on spermatogenesis, but natulan is characterized by the most significant toxic effect.

The patient appealed to a doctor in April 2018 with a desire to have a baby. There were complaints about impaired libido and erectile dysfunction. Analysis of spermogram showed a complete absence of spermatozoa in ejaculate (azoospermia). Hormonal blood test: FSH 14.79 mMe/ml (0.95—11.95), testosterone 25.53 nmol/l (12—35), inhibin B 65 pg/ml (42—392). There was reduced total volume of testes up to 14 cm³ (norm 30 cm³). Azoospermia caused by primary lesion of germinal epithelium after chemotherapy may be supposed considering high level of FSH combined with low level of inhibin B, as well as reduced testicular volume. Prospects for restoration of reproductive function are very doubtful. However, the patient has a chance to have genetic progeny considering presence of cryopreserved sperm in a cryobank.

**Conclusion**

Neurosurgeons, oncologists and radiologists should inform patients with brain tumors about the possible risk of hypogonadism, infertility and advisability of sperm cryopreservation. This approach increases the chance to have genetic progeny in the future.

Sperm cryopreservation is advisable in young patients, as well as in those who are interested for reproductive potential:
1) benign hypothalamic-pituitary tumors (pituitary adenoma, craniopharyngioma, etc.);

![Algorithm for fertility preservation in men with brain tumors.](image-url)
— with intact preoperative gonadotropic function and high risk of hypopituitarism (including hypogonadism);
— patients with hypogonadotropic hypogonadism after surgery, radiotherapy or drug treatment and restoration of sperm quality after gonadotropin therapy;
2) malignant brain tumors of any localization:
— prior to radio- and/or chemotherapy (Figure).
Preservation of fertility in men with benign and malignant brain tumors is a private, but urgent medical objective aimed at reduction of reproductive losses in these patients. It is necessary to develop the forms of informed consent of patients with proposal of cryopreservation if impaired fertility is supposed. It is advisable to conduct educational seminars for doctors whose specialties and possible methods of treatment are associated with the effect on fertility in men. Introduction of physician’s responsibility as a “subject of law” for the preservation of male fertility is necessary.

Authors declare no conflict of interests.

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Commentary

The authors noted that neurosurgery for CNS tumors, mainly hypothalamic-pituitary neoplasms, as well as chemo- and radiotherapy for brain malignancies of any localization can cause hypogonadism and infertility. Cryopreservation of spermatozoa is currently a reliable method to preserve male fertility increasing the chance to have genetic progeny in the future. However, there are still no standards for interaction between oncologists and specialists for reproductive technologies. Therefore, this article is relevant. The authors described the causes of reproductive disorders in patients with benign hypothalamic-pituitary tumors. Moreover, they emphasized that high incidence of hypogonadism in patients with hypothalamic-pituitary tumors is accompanied by a significant deterioration of quality of life, sexual and reproductive potential in men. There are no clear literature data about the feasibility of sperm cryopreservation in patients with benign hypothalamic-pituitary tumors. The authors showed the advantages of sperm cryopreservation in contrast to long-term treatment with gonadotropins. An important aspect of the article is information about reproductive disorders in patients with brain malignancies. These disorders can develop either during treatment, immediately after it or in long-term period. The authors reported 3 clinical cases with different severity of reproductive disorders.

O.G. Zheludkova (Moscow, Russia)

Commentary

Socially significant problem of infertility in men with brain tumors is considered in the article. Infertility may be potentially followed by destruction of family, impairment of the quality of life, including significant emotional and personal disorders. Patients with brain tumors usually appeal to a neurosurgeon. Neurosurgeon determines further tactics of diagnosis and treatment of a patient with brain tumor. Unfortunately, the majority of neurosurgeons do not always inform patients about possible reproductive disorders after removal of benign hypothalamic-pituitary tumors and during various modes of treatment of brain and spinal cord malignancies. Currently, cryopreservation of ejaculate, oocytes and embryos is considered as a standard method of preserving fertility in general oncology.

Neurosurgeon and oncologist should discuss with the patient of reproductive age all methods of fertility preservation before neurosurgery, chemo- and radiotherapy. Patient should be referred to a specialist for reproductive technologies if it is necessary.

Three case reports of benign and malignant brain tumors in men are presented in the article. Treatment of tumors was complicated by infertility in all cases. Sperm cryopreservation was carried out in 2 cases. Therefore, 1 patient has become a father.

The article is extremely important and interesting because modern and relevant issue of preservation of reproductive function in men with brain tumors is discussed for the first time.

A.Kh. Bekyashev (Moscow, Russia)
Treatment of Uncomplicated Vertebral Compression Fractures

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According to statistical studies in different countries, the annual incidence of spine and spinal cord injuries is 15—50 cases per 1 million people. In Russia, the incidence of this condition is 5% of the total number of all nonpenetrating traumatic injuries (Neurosurgery: Guidelines for Physicians, ed. by Prof. ON Dreval’, 2013). According to the WHO reports, approximately 500,000 people annually experience spine injuries worldwide. Acute spine injuries make up 23.7% of all spinal traumas and include contusions (2.67%), injuries to the capsular ligamentous apparatus (3.88%), fractures and dislocations (7.63%), and muscle injury (9.52%). In males, the risk of experiencing a spine injury is the highest at the age of 20—29 and above 70 years, while in women this risk is the highest at an age of 15—19 and above 60 years. According to the studies, this risk is characterized by an at least 2:1 ratio between adult males and females.

Objective — to compare the outcomes of surgical (vertebroplasty) and conservative treatment in management of pain syndrome in patients with uncomplicated spine injury.

Material and methods. The study involved 60 patients with stable uncomplicated compression fractures of vertebral bodies in the thoracic and lumbosacral spine. These patients were subdivided into two groups. Group 1 consisted of 30 patients who had undergone unilateral transpedicular percutaneous vertebroplasty; Group 2 involved 30 patients who had undergone a course of conservative treatment. The medical records and the catamnestic follow-up data of patients treated at the Neurosurgery Department of the Research Clinical Center of JSC Russian Railways in 2015—2017 were analyzed for this purpose.

Results. No statistically significant differences in sex, age, and level of injury were revealed between the study groups. A comparative analysis of treatment outcomes demonstrated that pain intensity assessed using the VAS scale was significantly reduced after one-year follow-up in both groups as compared to the baseline. A statistically significant decrease in pain intensity in the group of patients who had undergone vertebroplasty was observed as early as one month after the injury. No significant intergroup differences were observed in the long-term follow-up period (3 and 6 months) for this parameter. In five out of 60 patients, examination 12 months after the injury revealed that vertebral body height decreased by up to 10%. No statistically significant correlation with the treatment method was observed.

Conclusion. Vertebroplasty provides a statistically better pain relief during the first month after spine injury as compared to conservative treatment. For patients, this means earlier activation and quicker return to daily routines and work.

Keywords: pain syndrome, uncomplicated vertebral fractures, vertebroplasty.
group consisted of 30 patients who underwent percutaneous transpedicular unilateral vertebroplasty. Mean volume of bone cement injected during vertebroplasty ranged from 4.0 to 6.0 ml [8]. Postoperative immobilization in this group was achieved using rigid orthopedic corset for 1 month from surgery. Physical activity was also limited within 1 month. Non-steroidal anti-inflammatory drugs for 1 month and metabolites/muscle relaxants for 10 days after injury were prescribed in these patients.

The control group included 30 patients who received only conservative treatment including wearing of rigid orthopedic corset, medication and restriction of physical activity. Physical activity was limited for 3 months in the control group.

Preoperative examination in the main group included clinical survey, X-ray examination in two projections and computed tomography of the thoracic or lumbosacral spine depending on the level of injury [9]. Visual-analogue scale (VAS) was used to assess clinical effect of the treatment (0—10 scores). Testing was performed before surgery, at discharge, in 1, 3, 6, and 12 months after injury.

In the control group, patients were examined in the same way. Baseline data (VAS score) were obtained on the day of the primary outpatient examination. Follow-up examination was made in 1, 3, 6, and 12 months after injury.

Computed tomography and X-ray examination of thoracic or lumbosacral spine were carried out after 12 months in both groups to assess vertebral changes.

Statistical analysis was performed using SPSS 12.0 software package for Windows and Microsoft Excel 2007.

Results

There were 19 (31.7%) men and 41 (68.4%) women aged 35—76 years (mean 55 years) in both groups.

Age of patients undergoing surgery varied from 35 to 72 years (mean 53.4±5.03 years). In the control group, mean age was slightly older — 57.8±4.3 years (range 39—76 years). However, there were no significant differences between groups (p>0.5).

Lumbosacral spine injury was observed in 15 patients of the main group and in 17 patients of the control group (p>0.05). Thoracic spine fractures occurred in 15 patients of the main group and in 13 patients of the control group. Incidence of thoracic or lumbar spine fractures was similar in both groups.

Thus, there were no significant differences in sex, age and level of injury between both groups.

Patients in both groups experienced a significant relief of pain syndrome after 1 year of follow-up in comparison with baseline data. Significant relief of pain syndrome was already noted in 1 month after injury in the vertebroplasty group. Severity of pain syndrome was similar in both groups in long-term follow-up (3 and 6 months) (p>0.05) (Fig.).

There were no complications of vertebroplasty including bone cement dislocation outside the fracture zone with vein filling or spinal canal stenosis.

Reduced height of the vertebra by 10% was noted in 5 out of 60 patients in 12 months after injury. At the same time, this outcome did not significantly depend on the method of treatment. There were 2 (6.7%) patients in the vertebroplasty group and 3 (10%) patients in the control group (p>0.05). More severe pain syndrome was also noted in these patients (mean VAS score 5 after 12 months).

Osteopenia was diagnosed in 27 (45%) out of 60 patients, vertebral hemangiomas — in 15 (25%) patients including 6 patients with lesion of more than two levels. Nine (15%) patients required specific therapy for osteoporosis. Osteopenia and hemangiomas were significantly more common in the main group, that determined more active surgical approach in these patients (p<0.05). Repeated fractures were not observed in both groups.
Discussion

Predominance of women (68.4%) in our study is consistent with world trends. Spinal fractures in females are usually associated with menopause and osteoporosis. This correlation is due to the role of female sex hormones in calcium metabolism [10].

Vertebral changes in most patients once again confirm secondary nature of the absolute majority of spinal compression fractures. So, osteopenia or hemangioma were observed in 70% of patients in our sample. Significant role of these factors in the fracture mechanism may be assumed. Kinetic energy is enough to destroy spongy bone of the vertebra, but not enough to damage cortical layer of facet joints and severe disorders followed by neurological complications and vertebral instability.

Bone cement dislocation outside the fracture zone with vein filling or spinal canal stenosis is the most common complication of vertebroplasty described in the literature [11]. These events are likely to be associated with low viscosity of cement or violation of the technology of its injection. There were no such complications in our study.

Incidence of thoracic and lumbar spine fractures was similar in our study. However, greater incidence of compression fractures of thoracic spine is reported in the literature [1, 2]. This discrepancy may be associated with a small sample size in our study and strict exclusion criteria. In particular, these criteria were previous spinal fractures and lesion of more than one vertebral level.

Percutaneous vertebroplasty and conservative approach resulted similar outcomes. We observed similar 1-year results of treatment in both groups. However, there was a more significant relief of pain syndrome in 1 month after vertebroplasty. According to the literature, both approaches result similar 2-year outcomes [5—7]. Some authors associate vertebroplasty with an increased risk of fractures of the adjacent vertebrae in patients with osteoporosis [4]. However, there were no repeated injuries in both groups in our sample.

Some authors [12] criticize conservative approach for uncomplicated vertebral fractures due to decrease of vertebral body height with subsequent chronic pain syndrome. We have really noted 5 (8.3%) patients with reduced vertebral body height by 10% and more severe pain syndrome in 1 year after injury. However, there was no significant association of this complication with certain treatment strategy.

Conclusion

More significant relief of pain syndrome in 1 month after spinal injury follows vertebroplasty. This result means early activation and quick return to daily life and work for the patient.

VAS score is similar after vertebroplasty and conservative treatment in long-term period (3, 6 months and 1 year).

Authors declare no conflict of interests.

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Commentary

The article is interesting for those who are not seriously engaged in vertebroplasty. It has long been known that vertebroplasty and conservative treatment result similar long-term results. Indeed, vertebroplasty in acute period is followed by relief of pain syndrome in most patients (76—80%). As a rule, this is true for pathological vertebral fractures and fractures in patients with osteoporosis. However, there are no national trials with such design. This study is another evidence of similarity of vertebroplasty and conservative treatment for uncomplicated vertebral compression fractures regarding long-term results with more rapid relief of pain in early postoperative period.

A.A. Grin’ (Moscow, Russia)
The Effect of Various Multimodal Analgesia Regimens During Surgical Treatment of Patients with Spinal Stenosis on the Rate of Failed Back Surgery Syndrome

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**Objective** — to determine the effect of various methods of perioperative analgesia on the rate of failed back surgery syndrome in patients operated on for spinal stenosis.

**Materials and methods.** A total of 122 patients were operated on for spinal stenosis in 2010—2016. The patients were assigned to groups according to the type of received analgesia: Group K (n=19) underwent analgesia on-demand. Patients in the PMA group (n=21) received preventive multimodal analgesia (PMA) with ketoprofen, paracetamol and morphine. Patients in the PMA+PG (n=20) and PMA+N (n=20) groups additionally received pregabalin and nefopam, respectively. Patients in the PMA+E group (n=22) received continuous epidural analgesia with a combination of ropivacaine and morphine. In patients in the PMA+I group (n=20), the wound was infiltrated with ropivacaine and ketorolac.

**Results and conclusions.** In Group K, analgesia was not adequate during five postoperative days. Analgesia with PMA resulted in significant pain reduction during three postoperative days compared to Group K. Wound infiltration in addition to PMA was followed by more significant pain relief during six postoperative hours (compared to the PMA group). Administration of pregabalin or nefopam, as well as epidural analgesia, did not improve quality of postoperative analgesia. Five to seven months after the surgery, 66% (57; 75%) of patients had low back and/or leg pain; 41% (32; 50%) of patients had leg pain. Among patients suffering from pain, 32—41% patients had the severe chronic pain syndrome that resulted in sleep disorder, disability and significant deterioration of quality of life. The rate of failed back surgery syndrome did not depend on the perioperative analgesia regimen.

**Keywords:** spinal stenosis, lumbar fusion, pregabalin, nefopam, epidural analgesia, wound infiltration, postoperative analgesia, failed back surgery syndrome.

The decompressive laminectomy in a patient with spinal stenosis was performed by Lane in England in 1893, the first posterior spinal fusion procedure — by Briggs and Milligan in 1944 [1]. Since then, surgical technique has gone far ahead and the operations have become less traumatic. There was an increase of the number of spinal fusion procedures by 220% for the period from 1990 to 2010 [2]. However, 30—45% of operated patients experience pain in months and years after surgery. Long-standing pain syndrome in these patients often results anxiety and depressive disorders with an unproductive “avoidance” behavioral strategy (passive-suffering installation of the victim, drawn into the conflict by the circumstances). This condition complicates pain therapy [3]. The cost of treatment of these patients is high (about $ 19,000 per patient per year in the United States, there are no data for the RF). Moreover, impaired working capacity of patients is followed by increased financial burden on employable population [4]. Considering social significance of this problem, the term “failed back surgery syndrome” (FBSS) is used in the medical literature to account for these patients and improve quality of their treatment [5].

Thus, the purpose of this research was to study the effect of various methods of perioperative analgesia on FBSS incidence after surgery for spinal stenosis.

**Material and methods**

A prospective trial was made at the Sklifosovsky Research Institute for Emergency Care and approved by the local ethics committee. Follow-up period was 7 days from the day of surgery. Subsequent telephone interviewing was performed in 5—7 months after surgery. The study included patients aged 18—70 with spinal stenosis and ASA grade I—III (American Society of Anesthesiologists). All patients underwent elective decompression of neural structures and lumbar spine fusion surgery with cage and transpedicular system for the period 2010—2016. All procedures were made in the Department of Neurosurgery of the Sklifosovsky Research Institute for Emergency Care. In-hospital follow-up included 122 patients (55 men and 67 women). Then, 113 out of 122 patients were interviewed by telephone (3 patients were lost for follow-up, 1 patient refused to participate in the study, another 5 patients were excluded from the study due to redo spinal surgery).

Six different analgesic regimens were applied in study patients. Recruitment of patients in each subsequent group was begun after completion of the previous one (at least 20 people). Randomization was impossible due to the absence of all necessary consumables and medicines.
at the same time. The number of study patients in groups was different due to subsequent exclusion of some patients from the study, for example, due to non-compliance with the protocol or refusal of analgesics. Data collection was carried out by 3 researchers alternately at different time periods (G.P.G, D.N.S., E.A.A). Preventive multimodal analgesia (PMA) including ketoprofen, paracetamol and morphine was used in the 1st group (PMA group, \( n=21 \)). PMA and pregabalin (PG) were applied in the 2nd group (PMA + PG group, \( n=20 \)); PMA with nefopam (N) for one day after surgery — in the 3rd group (PMA + N group, \( n=20 \)); PMA and prolonged epidural analgesia (EA) with ropivacaine and morphine solution — in the 4th group (PMA + EA group, \( n=22 \)); PMA and intraoperative infiltration (I) of the wound with ropivacain solution and prolonged irrigation using ropivacaine and ketorolac solution — in the 5th group (PMA + I group, \( n=20 \)). Postoperative analgesia on demand was applied in the control group (C group, \( n=19 \)).

Exclusion criteria: 1) previous lumbar spine surgery; 2) difficult communication with a patient (language barrier, mental illness); 3) allergic reactions against certain analgesics; 4) contraindications to analgesics and methods of analgesia (acute gastroduodenal erosions and ulcers; liver and renal failure; exacerbation of chronic obstructive pulmonary disease, respiratory failure grade II—III; decompensated severe diabetes mellitus; chronic heart failure NYHA class 3—4; myocardial infarction within 1 month prior to surgery; alcohol abuse); 5) refusal to participate in the study. Patients were also excluded from the study in case of non-compliance with the protocol or refusal of analgesics. In the PMA + EA and PMA + I groups, patients were excluded from the study in case of intraoperative injury of dura mater, since regional methods of anesthesia were associated with risk of uncontrolled spinal block in these patients.

Baseline characteristics of patients (sex, age, body weight) were similar in all groups. However, between-group differences were noted in ASA class (Table 1). Unlike other groups, PMA + I group was characterized by no patients with ASA class 1, fewer patients with ASA class 2 and predominant patients with ASA class 3. This may be due to subjective assessment of ASA class (data for PMA + I group were collected by researcher E.A.A. who was not involved in data collection in other groups).

Study patients underwent spinal nerve decompression and spinal fusion surgery. There were no differences in spinal decompression, spinal fusion surgery by the cage, number of screws in fixation system and duration of surgery (Table 2). Operations were performed by 5 surgeons with individual experience of spinal surgery over 5 years.

All surgeries were performed under general anesthesia (induction — propofol 2 mg/kg and fentanyl 2 μg/kg, maintenance — 1 MAC of sevoflurane and nitrous oxide in combination with fractional administration of fentanyl, muscle relaxation — rocuronium bromide 0.6 and 0.15 mg/kg, respectively). Finally, patients were weaned from the ventilator in operating theatre and transferred to the intensive care unit after consciousness restoration. Anesthesia was conducted by a group of three anesthesiologists (G.P.G, E.A.A, D.N.S.) under the supervision of a senior anesthesiologist (G.P.G), who has many years of experience in neuroanesthesiology.

Scheme of postoperative analgesia was different in groups. Anesthesia on demand was applied in the control group. Medical staff of intensive care unit and neurosurgical department later chose certain analgesics. Metamizole sodium was injected in 16 (84%) patients, various non-steroidal anti-inflammatory drugs (NSAIDs) — in 17 (89%) patients, paracetamol — in 10 (53%) cases, tramadol — in 13 (68%) patients, promedol — in 8 (42%) patients, nalbuphine — in 3 (16%) cases and morphine in 1 (5%) patient. Excess of maximum single and/or daily doses of metamizol and NSAIDs was observed in 8 (42%) out of 19 patients. PMA was applied in the other groups. This regimen implied intravenous administration of ketoprofen 100 mg and paracetamol 1 g during wound closure, ketoprofen 100 mg per os every 12 hours and paracetamol 1 g intravenously every 6 hours for 3 postoperative days. Subject-regulated dosing of morphine was used in case of insufficient analgesia on the day of surgery. The next days, patients received ketoprofen 100 mg per os on demand (not more than 200 mg/day). In the PMA + N group, nefopam 20 mg (diluted in saline solution 200 ml) was intravenously administered 30 minutes before the end of surgery. Then, prolonged intravenous infusion of this drug (80 mg) was performed in ICU during the first postoperative day. In the PMA + PG group, pregabalin 300 mg per os was administered 1.5 hours before surgery and then 150 mg twice a day for 7 days. In the PMA + EA group, spinal fusion procedure was followed by insertion of the epidural catheter into the upper part of epidural space open after previous decompression. The catheter was passed cranially for 5 cm. As soon as aponeurosis was sutured, ropivacaine solution 0.35% 7 ml was injected into epidural catheter. The following measure was infusion of solution of ropivacaine 2 mg/ml and morphine 50 μg/ml through an elastomeric pump (rate 6 ml/hour). Postoperative infusion rate depended on subjective feeling of pain and ranged from 2 to 6 ml per hour.

In the PMA + I group, surgeon installed a perforated catheter for prolonged irrigation of the wound after spinal fusion procedure. This catheter was deployed under aponeurosis on the contralateral side. As soon as aponeurosis was sutured, ropivacaine solution 0.35% 7 ml was injected into the catheter with subsequent infusion of analgesic mixture of ropivacaine 2 mg/ml and ketorolac 0.15 mg/ml through elastomeric pump (rate 10 ml/hour). Postoperative infusion rate depended on subjective feeling of pain and ranged from 8 to 10 ml per hour. Closure of the wound was also associated with layer-by-layer in-
filtration of paraspinal muscles, subcutaneous fatty tissue and skin (ropivacaine solution 0.2% 3 mg/kg).

Severity of pain syndrome was assessed using a visual analogue scale (VAS) with range from 0 to 10 cm for no pain and unbearable pain syndrome, respectively. Pain syndrome was evaluated on the first postoperative day every 2 hours and within 2—7 days once a day. Anesthesia was considered as adequate if median of VAS value ranged 0—3 cm at rest and 0—4 cm for movements.

Presence and severity of pain in the back and leg was analyzed in 5—7 months after surgery during a telephone survey. The following answers were recorded: less than 2 days a week, more than 2 days a week, every day, permanent pain. Mean and maximum pain intensity was also determined using a numerical rating scale (NRS) from 0 to 10 (value 0 — no pain, value 10 — unbearable pain). Sensitive disorders in the lower extremities, pain-related sleep disorders and intake of analgesics were also evaluated (answers: “do not use”, “less than 2 days a week”, “more than 2 days a week”, “every day”). Influence of pain syndrome on the quality of life (answers: “does not affect”, “small influence”, “great influence”, “very great influence”) and employment status (answers: “I work”, “I do not work” “I do not work, as retired”) were also evaluated. Exclusion criterion was redo surgery within 6 months after inclusion in the study.

Statistical analysis data was performed using the Statistica 9.1 software package (StatSoft, Inc., USA). Quantitative variables are shown as medians and quartiles, qualitative values — absolute and relative frequencies. Quantitative characteristics in 6 independent groups were compared using Kruskal—Wallis ANOVA test. Two groups were compared using Mann—Whitney test, qualitative data — using χ2 and Fisher’s exact tests. We compared data in groups C (conventional anesthesia) and PMA (standard preventive anesthesia). Subsequent analysis included pairwise comparison of variables in PMA group and other groups (PMA + N, PMA + PG, PMA + EA, PMA + I). Differences were significant at p<0.05, for pairwise comparisons — 0.01 (with Bonferroni correction). A 95% confidence interval (CI) was calculated for some relative frequencies.

### Results and discussion

Control group was characterized by no adequate analgesia within 12 hours after surgery at rest and 5 postoperative days during movement. Other groups without regional anesthesia were also characterized by significant between-group differences in severity of pain syndrome (Table 3).

In the PMA group, analgesia was not adequate in 2 hours after surgery at rest, within 6 hours after surgery upon movement and on the 4th postoperative day. PMA + N group was characterized by inadequate analgesia within 4 hours after surgery at rest and 3 days upon movement, PMA + PG group — within 4 hours after surgery at rest and 6 hours upon movement.

In the PMA + EA group, analgesia was inadequate only 2 hours after surgery at rest and upon movement (Table 4).
Pain syndrome severity was significantly less in this group than in the PMA group only in 6 hours after surgery upon movement. There was a tendency (p<0.05) to a decrease of intensity of dynamic pain (compared to PMA group) after 4, 8 hours and on the 2nd day. Analgesia was adequate throughout entire follow-up period in the PMA + N group. There was a tendency (p<0.05) to a significant decrease of intensity of dynamic pain (compared to PMA group) only in 6 hours after surgery upon movement. There was no impairment of quality of life in every day. There was no impairment of quality of life in 30 (40%) patients. Mild, significant and extremely significant decrease of quality of life was observed in 19 (25%) and 11 (15%) patients, respectively. Sensitive disorders in the lower extremities in 6 months after surgery were reported by 62 (55%) out of 113 respondents. There were these disorders in 50 (44%) patients. Thirty-nine (35%) patients returned to full-time work, 8 (7%) patients were part-time employees. Thirty-five (31%) patients did not work due to retirement age, 30 (27%) ones did not return to work after surgery due to persistent pain syndrome. Thus, 30 (40%) out of 75 patients with pain syndrome in 6 months after surgery became disabled.

In conclusion, we would like to emphasize certain limitations of our study. These limitations are non-randomized study design, surgeries performed by several surgeons, anesthesia provided by various anesthesiologists and small number of patients in each group. We also did not take into account the role of risk factors (socio-demographic, psychological, clinical) in assessment of the results of surgical treatment in patients with herniated intervertebral discs. We will report these data in subsequent publications. Currently, we continue to search for

<table>
<thead>
<tr>
<th>Control period</th>
<th>Condition</th>
<th>Pain severity in study groups, Me (LQ, UQ)*, significance of differences, p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (n=19)</td>
<td>PMA (n=21)</td>
</tr>
<tr>
<td>2 h</td>
<td>Rest</td>
<td>6 (3;7)</td>
</tr>
<tr>
<td>4 h</td>
<td>Rest</td>
<td>6 (6.5;9)</td>
</tr>
<tr>
<td>6 h</td>
<td>Rest</td>
<td>5.75 (3;7.5)</td>
</tr>
<tr>
<td>8 h</td>
<td>Rest</td>
<td>6 (8;8.5)</td>
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<tr>
<td>10 h</td>
<td>Rest</td>
<td>5.5 (3;5.7)</td>
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<tr>
<td>12 h</td>
<td>Rest</td>
<td>7.5 (6;8)</td>
</tr>
<tr>
<td>2 days</td>
<td>Rest</td>
<td>4 (2;6.5)</td>
</tr>
<tr>
<td>3 days</td>
<td>Rest</td>
<td>6.5 (5;7)</td>
</tr>
<tr>
<td>4 days</td>
<td>Rest</td>
<td>4 (2.5;7)</td>
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<td>5 days</td>
<td>Rest</td>
<td>6.5 (5;7)</td>
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<tr>
<td>6 days</td>
<td>Rest</td>
<td>4 (2;6.5)</td>
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<tr>
<td>7 days</td>
<td>Rest</td>
<td>6.5 (6;8)</td>
</tr>
<tr>
<td>2 days</td>
<td>Rest</td>
<td>3 (1.5;7)</td>
</tr>
<tr>
<td>Movement</td>
<td></td>
<td>7.5 (4.5;9)</td>
</tr>
<tr>
<td>3 days</td>
<td>Rest</td>
<td>2.5 (2;4)</td>
</tr>
<tr>
<td>Movement</td>
<td></td>
<td>6 (4;8)</td>
</tr>
<tr>
<td>4 days</td>
<td>Rest</td>
<td>2 (1;4.5)</td>
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<tr>
<td>Movement</td>
<td></td>
<td>5 (2;5.7)</td>
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<tr>
<td>5 days</td>
<td>Rest</td>
<td>2 (1;5)</td>
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<tr>
<td>Movement</td>
<td></td>
<td>5 (1.5;8)</td>
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<tr>
<td>6 days</td>
<td>Rest</td>
<td>1.5 (1;4.5)</td>
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<tr>
<td>Movement</td>
<td></td>
<td>4 (2;9)</td>
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<tr>
<td>7 days</td>
<td>Rest</td>
<td>1 (1;3.5)</td>
</tr>
<tr>
<td>Movement</td>
<td></td>
<td>3 (2.7)</td>
</tr>
</tbody>
</table>

Footnote: *— median and quartiles; p¹ — comparison of the С and PMA groups using Mann—Whitney test; p² — comparison of the PMA and PMA + N groups using Mann—Whitney test; p³ — comparison of the PMA and PMA + PG groups using Mann—Whitney test.
effective methods of analgesia for patients undergoing spinal surgery.

Conclusions

1. Subject-regulated dosing of analgesics is followed by inadequate analgesia in at least 50% of patients with spinal stenosis within 5 days after decompression of neural structures and spinal fusion surgery. Preventive multimodal analgesia including ketoprofen, paracetamol and morphine results more significant relief of postoperative pain within 3 days after surgery in comparison with analgesia on demand.

2. Intraoperative infiltration of the wound with ropivacaine solution and prolonged postoperative irrigation with analgesic mixture of ropivacaine and ketorolac in addition to preventive multimodal anesthesia result even more significant (in comparison with PMA) relief of postoperative pain syndrome within 6 hours after decompression of neural structures and spinal fusion surgery.

3. Pregabalin and nefopam, as well as epidural analgesia with solution of ropivacaine and morphine in the

<table>
<thead>
<tr>
<th>Table 4. VAS score of pain syndrome in groups PMA, PMA + EA and PMA + I</th>
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</thead>
<tbody>
<tr>
<td>Control period</td>
</tr>
<tr>
<td>2 h</td>
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<tr>
<td>Movement</td>
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<tr>
<td>4 h</td>
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<td>Movement</td>
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<td>6 h</td>
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<td>Movement</td>
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<tr>
<td>6 days</td>
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<td>Movement</td>
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<tr>
<td>7 days</td>
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<td>Movement</td>
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</tbody>
</table>

Footnote. *— median and quartiles; p^1 — comparison of the PMA and PMA + EA groups using Mann—Whitney test; p^2 — comparison of the PMA and PMA + I groups using Mann—Whitney test.

<table>
<thead>
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<th>Table 5. Characteristics of pain syndrome in 5—7 months after surgery</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>C (n=16)</td>
</tr>
<tr>
<td>PMA (n=21)</td>
</tr>
<tr>
<td>PMA+N (n=17)</td>
</tr>
<tr>
<td>PMA+PG (n=18)</td>
</tr>
<tr>
<td>PMA+EA (n=22)</td>
</tr>
<tr>
<td>PMA+I (n=19)</td>
</tr>
<tr>
<td>p</td>
</tr>
</tbody>
</table>

Footnote. p — significance of between-group differences; * — median and quartiles; 1 — comparison of groups using χ^2 test; 2 — comparison of groups using Kruskal—Wallis ANOVA test.
scheme of preventive multimodal analgesia are not followed by improved quality of postoperative analgesia.

4. Back and/or leg pain is observed in 66% of patients in 5—7 months after surgery for spinal stenosis, leg pain — in 41% of patients. In 32—41% of patients, severe chronic pain syndrome results in sleep disturbances, disability and significant aggravation of quality of life.

5. Incidence of failed back surgery syndrome after operations for spinal stenosis did not depend on the perioperative analgesia scheme.

REFERENCES


Authors’ participation:
Concept and design of the study — P.G, V.T.
Collection and analysis of data — P.G., N.D., A.E.
Statistical analysis — P.G., O.R.
Writing the text — P.G.
Editing — V.T., A.G., O.R.

Authors declare no conflict of interests.

Commentary

It is well known that pain is the main reason for treating a patient with spinal pathology to a neurosurgeon [1]. Therefore, pain relief is one of the main effects expected from neurosurgical intervention while postoperative chronic pain syndrome instead of pain relief is very disheartening situation. This result is determined as “failed back surgery syndrome” in modern literature. Moreover, there are over 9000 publications devoted to this problem in the PubMed database that clearly indicates its relevance in the world. This article is devoted to the same problem.

The authors have done a serious job. Analysis included 122 patients who underwent surgery in one of the leading neurosurgical clinics of our country over 7-year period. The hypothesis tested by the authors is quite simple and concrete. Is there correlation between the effectiveness of perioperative analgesia and incidence of failed back surgery syndrome? It should be recognized that the authors received a quite convincing answer. There is no correlation. I will say right away that this conclusion is somewhat different from the generally accepted point of view [2—6]. Nevertheless, a result is presented to us and we must consider it.

I have no any serious remarks regarding design of the study, methods of research and statistical analysis. However, I was personally somewhat embarrassed by the following aspects.

1. A rather high incidence of failed back surgery syndrome (32—41%). This value is significantly higher than in one recent publication [7]. Therefore, the reasons of such difference are discussable. Unfortunately, the authors did not comprehensively analyze this result. In addition, list consisting of six references looks quite modest.

2. Positive effect of postoperative analgesia with gabapentinoids. There are certain trials devoted to these drugs administered in sufficiently high doses (1,200 mg) and according to a pre-emptive scheme (even a week prior to surgery in one study) [8]. However, there was no serious analgesic effect compared with the basic scheme of analgesia (subject-regulated intravenous morphine administration). Only a very moderate decrease of the required dose of morphine and reduced incidence of undesirable effects of opiates were observed. Similar data were obtained in other works [9—13].

3. Conversely, no serious analgesic effect of epidural anesthesia. These results are especially difficult for me to perceive for two reasons. The first cause is world literature data. These data are also interesting in their own way. There is a relatively small number of publications devoted to intraoperative and postoperative epidural analgesia [14—19]. Various authors report the use of epidural anesthesia only for postoperative analgesia after spinal neurosurgery (one or two epidural catheters depending on wound dimension are installed by neurosurgeon under visual control prior to suturing of the wound) [14, 20—23]. It is important that general conclusion of all these works is simple. There is nothing more effective than epidural anesthesia. Moreover, there are additional benefits associated with effective analgesia and refusal of opiates including fast rehabilitation of patient and no problems with intestinal motility and urination. The second reason is our own experience of these procedures [24—26]. I did not understand why the authors obtained opposite data.

In conclusion, I would like to say that the research turned out to be interesting, useful and worthy of discussion. It is essential for further analysis of this actual and unresolved problem.

A.Yu. Lubnin (Moscow, Russia)
The Impact of Spinopelvic Parameters on the Rate of Adjacent Segment Instability After Short-Segment Spinal Fusion

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1R.R. Vreden Russian Research Institute of Traumatology and Orthopedics, St. Petersburg, Russia; 2Burdenko Neurosurgical Institute, Moscow, Russia

Objective. The objective of this study is to determine the impact of postoperative spinopelvic parameters on the development of adjacent segment instability after single-level lumbar fusion.

Material and methods. A total of 116 patients with degenerative spine conditions after lumbar fusion were enrolled in this study and subdivided into two groups. Group I consisted of 24 patients with signs of adjacent segment instability; Group II included 92 patients without signs of instability. The minimal follow-up period was 24 months.

Results. The mean postoperative lumbar lordotic (LL) angle in both groups was within the normal range (−60.9±12); no statistically significant intergroup differences were revealed (56.6±12.1 and 58.4±11.2 for Groups I and II, respectively; \( p = 0.314 \)). In Group I patients, the mean pelvic incidence (PI) angle differed significantly from the mean PI values in Group II patients (70.4±7.6 and 53.2±8.4, respectively; \( p = 0.006 \)) and from the normal PI values (51.9±10). Therefore, the mean difference between PI and LL (PI—LL) angles in the Group I patients was significantly higher than in Group II (16.2±5.4 and 4.8±8.6, respectively; \( p = 0.004 \)). Significant PI—LL mismatch (PI—LL ≥10°) was observed in 22 (91.7%) patients in Group I and in 11 (11.95%) patients in Group II.

According to regression analysis data, the PI—LL mismatch was identified as a risk factor for adjacent segment instability; the odds ratio =4.2; 95% confidence interval 1.46—12.25; and \( p = 0.007 \).

Conclusion. Patients with the high PI value and low LL value have a significantly higher risk of adjacent segment instability after short-segment spinal fusion.

Keywords: lumbar fusion, adjacent segment disease, spinopelvic parameters, sagittal balance, spinal fixation, spinal instability.

Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>VMS</td>
<td>vertebral-motor segment</td>
</tr>
<tr>
<td>LL</td>
<td>lumbar lordosis</td>
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<tr>
<td>PI</td>
<td>pelvic incidence</td>
</tr>
<tr>
<td>(PI—LL)</td>
<td>difference of pelvic incidence and lumbar lordosis</td>
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<tr>
<td>PT</td>
<td>pelvic tilt</td>
</tr>
<tr>
<td>SS</td>
<td>sacral slope</td>
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<tr>
<td>SVA</td>
<td>sagittal vertical axis</td>
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</table>

Currently, surgical approach is preferred for severe degenerative-dystrophic lesion of lumbar spine. The main purposes of surgery are decompression of neural structures and prevention of instability of the vertebral-motor segments (VMS). In this case, transpedicular fixation with anterior spondylodesis via posterior approach is the most common method of stabilization (so-called rigid fixation at 360°). However, there is a risk of unsatisfactory long-term results despite successful spondylodesis with instrumental fixation. Decompensation of degenerative lesion of adjacent PDS is important factor (so-called adjacent segment disease). At the same time, instability of adjacent PDS is the most significant lesion requiring surgical treatment with increased length of instrumental fixation.

To date, various factors contributing to emergence and progressive development of degenerative lesion of adjacent PDS have been described. According to classical studies, these factors are divided into two main categories: 1) patient-associated factors usually independent of the doctor; 2) surgical factors, which can be directly influenced by the doctor during surgery [1—5].

Patient-associated factors are female sex, age over 60 or under 30 years, body mass index over 30 kg/m², smoking, concomitant diseases, previous degenerative changes of adjacent interbody discs, menopause. Surgical factors are significant length of fixation, involvement of L5—S1 segment into spondylodesis, implant stiffness, technical errors of fixation, sagittal and frontal balance disorders.

Currently, there is no consensus regarding essential role of certain risk factors of degenerative changes in adjacent VMS [3, 5—7]. Sagittal imbalance and disorders of spinopelvic parameters are discussed most widely in the modern literature [8, 10]. In this discussion, there are only a few works analyzing dependence of degenerative lesions in adjacent PDS and degree of violation of spinopelvic parameters. For example, M. Senteler et al. [8] and D. Rothenfluh et al. [9] showed that violation of certain spinopelvic parameters results early development of adjacent segment syndrome.

However, other risk factors should be excluded to determine significant impact of disorders of spinopelvic parameters on the development of adjacent segment syn-
drome. Some recent reports confirmed significance of some spinopelvic parameters in the development of adjacent segment syndrome. However, there are no trials devoted to the analysis of isolated impact of spinopelvic parameters on the rate of adjacent segment instability.

**Material and methods**

A retrospective study included 148 patients with degenerative-dystrophic lesion of lumbar spine who underwent short-segment spondylodesis with anterior interbody spondylodesis via posterior approach in 2006—2013. VMS stabilization was carried out using interbody cages and rigid system for transpedicular fixation.

In all patients, spinopelvic parameters were evaluated prior to surgery, immediately after surgery. Moreover, data of X-ray examination were considered after 3, 6, 12 and 24 months.

Results of clinical and X-ray examination and MRI data were evaluated in all cases. Instability in adjacent segments was assessed using X-ray scans of lumbar spine in lateral projection with maximum flexion and extension.

Patients with the most discussed risk factors of degenerative lesion of adjacent segment were excluded from further analysis. These were patients with overweight (body mass index over 30 kg/m²), severe degenerative lesion of adjacent intervertebral disc and severe violation of sagittal imbalance. Moreover, patients with progressive degenerative lesion (spondylarthrosis and spinal stenosis), as well as infectious process and instability of metal structures were also excluded.

Thus, the final cohort for analysis of the impact of spinopelvic parameters on the rate of adjacent segment instability consisted of 116 patients.

Instability of adjacent segments in long-term postoperative period was observed in 24 (16.2%) patients within the entire follow-up period (3—10 years). These patients were enrolled into the 1st group. There were cases of VMS instability below fusion area. Group 2 consisted of 92 patients without this event.

We considered values of lumbar lordosis (LL), pelvic tilt (PT), pelvic incidence (PI) and displacement of sagittal vertical axis (SVA) using lateral X-ray scans in standing position. Moreover, difference of pelvic incidence and lumbar lordosis (PI—LL) was calculated for all patients.

Statistical analysis was performed using multiple logistic regression and ROC analysis. Differences were significant at $p<0.05$.

**Results**

We revealed significant between-group differences in PI, PI—LL and PT values using standard non-parametric statistical methods. So, mean postoperative values of PI in the group 1 (PI =70.4°±7.6°) were significantly different from those in the group 2 (PI =53.2°±8.4°) and normative values in the literature (PI =51.9°±10°). There were higher values of PI—LL and PT in the 1st group compared with the 2nd group. A significant difference of pelvic incidence and lumbar lordosis (PI—LL >10°) was observed in 22 (91.7%) patients of the 1st group and 12% of patients of the 2nd group.

Data of comparison of groups 1 and 2 are shown in Table 1.

---

**Table 1. Spinopelvic parameters and adjacent segment syndrome**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Group with adjacent segment instability (n=24)</th>
<th>Group without adjacent segment instability (n=92)</th>
<th>Reference value*</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>70.4°±6°</td>
<td>53.2°±8.4°</td>
<td>51.9°±10°</td>
<td>0.006</td>
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<tr>
<td>PT</td>
<td>18.2°±7.1°</td>
<td>13.3°±8.4°</td>
<td>13°±6°</td>
<td>0.044</td>
</tr>
<tr>
<td>LL</td>
<td>−56.3°±12.1°</td>
<td>−58.4°±11.2°</td>
<td>−60.9°±12°</td>
<td>0.314</td>
</tr>
<tr>
<td>PI—LL</td>
<td>16.2°±5.4°</td>
<td>4.8°±8.6°</td>
<td>−8°±9°</td>
<td>0.004</td>
</tr>
<tr>
<td>PI—LL &gt;10°</td>
<td>9.17</td>
<td>12</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>SVA, mm</td>
<td>42±14</td>
<td>38±17</td>
<td>−0.5±25</td>
<td>0.146</td>
</tr>
</tbody>
</table>

*Footnote: *— F. Schwab et al., 2010.

**Table 2. Univariate analysis of risk factors of adjacent segment instability.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>$p$</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>0.007</td>
</tr>
<tr>
<td>LL</td>
<td>0.112</td>
</tr>
<tr>
<td>PI—LL</td>
<td>0.005</td>
</tr>
<tr>
<td>PT</td>
<td>0.047</td>
</tr>
<tr>
<td>SVA</td>
<td>0.319</td>
</tr>
</tbody>
</table>

**Table 3. Multiple logistic regression data**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>$p$</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>0.067</td>
<td>1.2 (0.92—1.65)</td>
</tr>
<tr>
<td>PI—LL</td>
<td>0.007</td>
<td>4.2 (1.46—12.25)</td>
</tr>
<tr>
<td>PT</td>
<td>0.087</td>
<td>1.1 (0.96—1.45)</td>
</tr>
</tbody>
</table>
Initially, we identified the factors associated with adjacent segment instability for the entire follow-up period using univariate analysis and logistic regression. These factors were PI, PI—LL and PT (Table 2).

Further, we used ROC-analysis and multiple logistic regression to analyze the role of certain of above-mentioned risk factors in the development of adjacent segment instability (Table 3).

Multiple logistic regression analysis showed that only difference of pelvic incidence and lumbar lordosis (PI—LL) was a significant predictor of instability of adjacent VMS. PI—LL value over 11 is a significant risk factor of this lesion ($p=0.007; \ OR\ 4.2; \ 95\%\ CI\ 1.46—12.25$) (Table 3).

The threshold value of PI—LL (12) was determined using ROC curve ($p=0.017, \ AUC\ 0.633, \ 95\% \ CI\ 0.54—0.72$) (Figure).

Thus, according to ROC-analysis and multiple logistic regression, risk of adjacent segment instability is increased by 4.2 times in case of PI—LL 12 and over. This value was determined using Youden index with sensitivity of 27.8 and specificity of 91.7.

**Discussion**

Some authors [11] consider that global balance of spine is the most important predictor of satisfactory long-term postoperative results. However, assessment of sagittal spinal profile is often carried out considering only lumbar lordosis and SVA displacement. At same time, preoperative analysis of spinopelvic parameters is not a trivial study and not always performed by surgeons, especially in case of normal lumbar lordosis and SVA.

Isolated analysis of pelvic parameters does not reflect true biomechanics of spinopelvic ratios. Analysis of above-mentioned characteristics as a whole is essential for objective assessment of compensatory resources of spine.

Difference of pelvic incidence and lumbar lordosis is considered to be one of the most significant spinopelvic parameters in degenerative lesion of lumbar spine [8, 9]. So, M. Senteler et al. [8] showed that spinopelvic ratios quantitatively expressed in PI—LL value correlate with load on facet joints in segments L3—L4 and L4—L5.

In this study, we found a significant correlation of PI—LL and probability of adjacent segment instability syndrome in the absence of other risk factors. It should be noted that isolated violations of PI and LL were not significant risk factors of adjacent segment instability. Differences of these values was crucial as the main compensatory mechanism opposing the axial load.

Currently, multiple biomechanical studies confirm advanced load on overlying VMS after lumbar spine fusion surgery [12—14]. However, overload of these seg-
ments results degenerative lesions only in some cases. Certain risk factors including overweight, previous degenerative changes in intervertebral disc and positive sagittal imbalance are essential for degeneration [14—16]. We excluded these risk factors and revealed X-ray signs of instability of overlying VMS after short-segment spinal fusion surgery in 20.6% of cases. Multivariate analysis of spinopelvic ratios was valuable to determine an important predictor of degenerative lesion in the entire cohort of patients. Some authors [17—19] consider that PI—LL value characterizes ability of spine to withstand axial load. Thus, overload of adjacent segments on the background of low compensatory spinal capabilities may be followed by degenerative spinal lesion.

Conclusion

Thus, patients after short-segment spinal fusion surgery have a high risk of degenerative lesion of adjacent segments in the presence of violations of spinopelvic parameters. The same is true for patients without global spinal imbalance and deficit of lumbar lordosis. Postoperative PI—LL value over 12 should be considered as a sign of latent spinal deformation associated with a high risk of adjacent segment degeneration.

Authors’ participation:

Concept and design of the study — D.P., N.K.
Collection and analysis of data — S.M., I.V.
Statistical analysis — S.M.
Writing the text — S.M.
Editing — I.V.

Authors declare no conflict of interests.

REFERENCES


Received: 24.04.18
Management of Complex Skull Base Defects Accompanied by Pneumocephalus

E.V. SHELESKO*, D.N. KAPITANOV, A.D. KRAVCHUK, V.A. OKHLOPKOV, O.S. ZAYTSEV, N.A. CHERNIKOVA

Burdenko Neurosurgical Institute, Moscow, Russia

Aim — the study aim was to analyze our own experience in treating patients with complex skull base defects accompanied by pneumocephalus and, based on the findings, to develop an optimal treatment approach for this pathology.

Material and methods. We retrospectively reviewed a series of 30 patients with complex skull base defects accompanied by pneumocephalus who underwent inpatient treatment at the Burdenko Neurosurgical Institute in the period from 2001 to 2017. We analyzed demographic characteristics of patients (gender, age), clinical data (etiology, somatic and neuropsychiatric status, radiological data), and treatment aspects (conservative or surgical treatment, used approach, defect characteristics, reconstructive materials). Treatment outcomes were assessed based on analysis of changes in clinical manifestations, postoperative complications, and recurrences. The obtained data were compared to the results of literature review.

Results. In the series of 30 patients with complex skull base defects accompanied by pneumocephalus, the mean age was 41 years (range, 17—68 years); there were 17 (59%) males and 13 (41%) females. Etiologically, there were 17 (59%) traumatic cases, 11 (36%) iatrogenic cases, and 2 (5%) spontaneous cases. Clinically, the patients presented with the following manifestations: psychiatric-neurological symptoms (41%), nasal cerebrospinal fluid (CSF) leak (36%), impaired consciousness (27%), and meningitis (23%). Eight patients with acute injuries underwent complex conservative treatment that included infusion, and anti-edema, vascular, metabolic, anticonvulsant, and antibacterial therapy. In cases of conservative treatment failure or tension pneumocephalus accompanied by abrupt worsening of the patient's condition, surgical treatment was used. A total of 24 interventions (including revision surgery) were performed in 22 patients. All patients underwent endoscopic endonasal reconstruction of complex skull base defects. Tissues used for reconstruction included the fascia lata and adipose tissue (77%), fascia lata and cartilage/bone from the nasal septum (14%), and a pedicled nasoseptal flap (9%). The success rate of reconstructive interventions was 91%. There were 2 (9%) recurrences. Postoperative complications in the form of meningitis occurred in 4 (18%) patients.

Conclusions. In the case of a nasal cerebrospinal leak history and worsening of the patient’s condition accompanied by common cerebral and psychiatric symptoms, the development of pneumocephalus should be considered first, the early diagnosis of which will facilitate choosing the correct treatment approach. In the case of acute injury in patients with the established diagnosis of pneumocephalus caused by gas-forming infection, conservative therapy is indicated in the early period after neurosurgical interventions with opening of the meninges. Tension pneumocephalus together with a skull base bone defect (according to CT) and a nasal CSF leak history is the indication for surgical treatment. In this case, the endoscopic endonasal technique is the method of choice.

Keywords: pneumocephalus, nasal cerebrospinal fluid leak, endoscopic endonasal surgery, skull base surgery.

Abbreviations:
CT — computed tomography
TBI — traumatic brain injury

Pneumocephalus is the presence of air within the cranial cavity. The most common cause of pneumocephalus is traumatic injury of bones and soft tissues of skull base and cranial vault as a result of neurosurgery (20.6% of all chiasmal-sellar procedures) and traumatic brain injury (TBI) (0.5—1.0% of all TBIs) [1]. Tumors or infections are sometimes accompanied by pneumocephalus. Spontaneous pneumocephalus is extremely rare [2].

There are two main theories of pathogenesis of pneumocephalus. The first one was described by M. Dandy [3] in 1926. This theory is known as ball valve mechanism and determines intracranial spread of air through a skull base defect in case of external overpressure in relation to intracranial pressure (for example, during sneezing, etc.). The second theory proposed by M. Horowitz [4] in 1964 is called as "inverted pop bottle syndrome". Profuse nasal luerorrhea followed by negative intracranial pressure is associated with intracranial spread of air through a damaged dura mater. Volume of the air is proportional to the volume of lost cerebrospinal fluid.

Tension pneumocephalus is a life-threatening event because acute intracranial hypertension syndrome may be followed by brainstem herniation and compression of vital structures. Hypertension is a result of rapid accumulation of air within the cranial cavity [5, 6].

Pneumocephalus may be accompanied by meningitis and other inflammatory complications, since there is an advanced risk of intracranial infectious contamination in this case [7].

Clinical symptoms of pneumocephalus depend on localization and volume of air within the cranial cavity. The most common symptoms are headache, epileptic seizures, dysfunction of the cranial nerves, sensation of splashing noise and cracking in the head, meningism, impaired consciousness, psychopathological and other disorders [8]. Tension pneumocephalus may be associated with signs of brainstem dislocation. The "gold stan-

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dard” for diagnosing pneumocephalus is computed tomography (CT). Air is revealed under meninges, in brain matter and ventricles (Fig. 1) [9].

There is a pathognomonic CT-symptom of tension pneumocephalus. It is so-called Mount Fuji sign — presence of gas between the tips of the frontal lobes followed by their compression (Fig. 2) [10].

Material and methods

A retrospective analysis included 30 patients with skull base defect followed by pneumocephalus. All patients were treated at the Burdenko Neurosurgery Center for the period from 2001 to 2017. Demographic characteristics of patients (sex, age) and clinical data (etiology, somatic and neurological status, radiological data) were studied. Complex conservative treatment was applied in 8 patients with acute TBI. There were 24 operations (including recurrences) in 22 patients. All patients underwent endoscopic endonasal repair of skull base defect. Various aspects of surgical treatment were evaluated (characteristics of the defect, plastic materials, intraoperative use of navigation). Follow-up period ranged from 1 month to 16 years (median 8 years). Analysis of surgical results implied assessment of clinical manifestations, postoperative complications and recurrences. Our own results were compared with literature data.

Results

Mean age of patients was 41 years (range 17—68). There were 17 (59%) men and 13 (41%) women. Pneumocephalus had various causes. Traumatic pneumocephalus was observed in 17 (59%) patients including 9 cases of injuries after road accidents, 6 cases of household injuries and 2 cases of sports injuries. Iatrogenic pneumocephalus was observed in 11 (36%) patients including 7 cases of skull base malignancies and 4 patients after endoscopic endonasal surgery. There were 2 (5%) cases of spontaneous pneumocephalus. Major symptoms of pneumocephalus were headache ($n=30, 100\%$), nasal liquorhea ($n=19, 64\%$), neuropsychiatric symptoms ($n=12, 41\%$), impaired consciousness ($n=8, 27\%$). Previous meningitis was noted in 5 (17\%) patients (Table 1).

Eight patients with acute injuries required complex conservative treatment including infusion, anti-edema, vascular, metabolic, anticonvulsant and antibacterial therapy. The main goal of this treatment was relief of meningeal and hypertensive syndromes. Vascular therapy

Fig. 1. CT-scans of the patient after repeated removal of astrocytoma of the right hemisphere. a — frontal plane; b — sagittal plane. Air accumulation within the anterior cranial fossa and in the brain ventricles.

Fig. 2. CT-scan (axial plane). Mount Fuji sign: a large accumulation of air with compression of frontal lobes.
was aimed at accelerating air resorption and restoring normal intracranial volumes.

Surgical approach was preferred for tension pneumocephalus accompanied by deterioration of vital functions. There were 24 surgeries (including recurrences) in 22 patients. All patients underwent endoscopic endonasal repair of skull base defect. Defect of ethmoid labyrinth was observed in 8 (36%) patients, frontal sinus — in 6 (27%) cases, sphenoid sinus — in 5 (23%) cases, lamina cribrosa — in 3 (14%) patients. Three (14%) patients had multiple defects. Fascia lata and fat as plastic materials were used for repair of defect in 17 (77%) patients, fascia lata and cartilage/bone of nasal septum — in 3 (14%) cases, pedicled nasoseptal flap — in 2 (9%) patients. Repair was successful in 91% of cases. There were 2 recurrences (9%). Postoperative complications (meningitis) occurred in 4 (18%) patients. Medtronic Fusion navigation system was applied in 3 (14%) patients. Postoperative antibiotic therapy was administered in all patients. Postoperative regression of pneumocephalus was analyzed considering clinical manifestations and CT data (after 3—5 days).

**Discussion**

A series of 30 cases of pneumocephalus is reported in the article. It is a rare complication of skull base defect associated with nasal liquorhea.

We have found 15 articles devoted to pneumocephalus in the Medline database for the period from 1998 to 2016. These data are summarized in Table 2 [12—26]. The largest sample includes 11 cases.

In our sample, pneumocephalus was predominantly caused by trauma (n=17, 59%). In these cases, profuse nasal liquorhea resulted negative intracranial pressure and intracranial passage of air through the skull base defect. Protective mechanism of cerebrospinal fluid hyperproduction does not have time to form at this stage. Thus, inverted pop bottle mechanism prevails in the pathogenesis of pneumocephalus.

Pneumocephalus is most likely caused by ball valve mechanism in case of iatrogenic nasal liquorhea (intracranial spread of air through a skull base defect in case of external overpressure in relation to intracranial pressure during snottting, sneezing and other conditions). This theory is more probable due small defects in these cases and behavioral postoperative disorders.

Previous long-standing nasal liquorhea (within 1.6 and 2 years) was noted in 2 cases of spontaneous pneumocephalus. Moreover, nasal liquorhea was later complicated by deterioration of neuropsychiatric symptoms and confirmed pneumocephalus. Perhaps, these patients with liquorhea and previous infection (a history of fever and headaches without clinical confirmation of meningitis and no in-hospital treatment) had impaired protective mechanism of hyperproduction of cerebrospinal fluid that was followed by negative intracranial pressure and entering air.

Correlation of etiology and pathogenesis of pneumocephalus was not analyzed in those reports assessed by us. Probably, this is due to small sample size. H. Kim et al. [24] reported a rare case of pneumocephalus as a result of gas-forming infection (pneumococcal meningitis). There were no such cases in our sample.

Pneumocephalus is characterized by various symptoms: headache, nasal liquorhea, nausea, vomiting, meningism, dysfunction of the cranial nerves, impaired consciousness. A special clinical aspect is psychopathological symptoms. This is confirmed in our research and by other authors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>age: years, mean (range)</td>
<td>41 (17—68)</td>
</tr>
<tr>
<td>male</td>
<td>17 (59)</td>
</tr>
<tr>
<td>female</td>
<td>13 (41)</td>
</tr>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
</tr>
<tr>
<td>nasal liquorhea</td>
<td>19 (64)</td>
</tr>
<tr>
<td>neuropsychiatric symptoms</td>
<td>12 (41)</td>
</tr>
<tr>
<td>impaired consciousness</td>
<td>8 (27)</td>
</tr>
<tr>
<td>previous meningitis</td>
<td>5 (17)</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td></td>
</tr>
<tr>
<td>traumatic</td>
<td>17 (59)</td>
</tr>
<tr>
<td>road accident</td>
<td>9 (53)</td>
</tr>
<tr>
<td>household injury</td>
<td>6 (35)</td>
</tr>
<tr>
<td>sports trauma</td>
<td>2 (12)</td>
</tr>
<tr>
<td>iatrogenic</td>
<td>1 (36)</td>
</tr>
<tr>
<td><strong>Iatrogenic:</strong></td>
<td></td>
</tr>
<tr>
<td>removal of skull base malignancy</td>
<td>11 (36)</td>
</tr>
<tr>
<td>endoscopic endonasal surgery</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4 (36)</td>
</tr>
<tr>
<td></td>
<td>2 (5)</td>
</tr>
</tbody>
</table>
### Table 2. World data regarding treatment of skull base defects complicated by pneumocephalus

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Localization of defect</th>
<th>Cause</th>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Jung-Sap Lee et al., 2010 [19]</td>
<td>1</td>
<td>Frontal and sphenoid sinuses</td>
<td>Spontaneous</td>
<td>Headache, nausea</td>
<td>Medication</td>
</tr>
<tr>
<td>15. Baba M., 2016 [26]</td>
<td>1</td>
<td>Sphenoid sinus</td>
<td>Spontaneous</td>
<td>Headache, liquorrhea</td>
<td>Surgery</td>
</tr>
<tr>
<td>Our sample</td>
<td>30</td>
<td>8 — multiple defects, 8 — ethmoid cells, 6 — frontal sinus, 5 — sphenoid sinus, 3 — lamina cribrosa</td>
<td>17 — traumatic, 11 — iatrogenic, 2 — spontaneous</td>
<td>Headache, mental disorders, impaired consciousness, liquorrhea</td>
<td>Medication in 8 patients, surgery in 22 patients</td>
</tr>
</tbody>
</table>
J. Simmons and A. Luks [11] described disorders of mental status in pneumocephalus. They found that only 2 ml of intracranial air may be associated with psychiatric symptoms. According to these authors, large volume of intracranial air resulted tension pneumocephalus with drowsiness, blockade of spontaneous activity and impaired consciousness. Moderate pneumocephalus usually results "frontal symptoms" — environmental disorientation, cognitive disorders, apato-abulic syndrome. These disorders are caused by pneumocephalus within the anterior cranial fossa and compression of frontal lobes.

According to our observations, successful treatment followed by regression of pneumocephalus result a positive dynamics in the mental status. Improvement of consciousness and relief of apato-abulic syndrome are followed by the next stage of recovery of mental activity (disintegrated consciousness).

Treatment strategy (medication or surgery) depends on etiology, volume of intracranial air and clinical picture of pneumocephalus. G. Satyarthee and A. Mahapatra [16] reported two cases of pneumocephalus after previous surgery for pituitary adenoma. Conservative approach was applied in both cases (bed rest, antibiotic and symptomatic therapy). One patient required surgery later (endoscopic repair of skull base defect). Gas-forming infection followed by pneumocephalus should be always managed with medication and adequate antibacterial therapy.

Skull base defect and ineffective medication require surgical closure of the defect. Endoscopic endonasal surgery was used in most cases (analysis of 12 articles). In our sample, this procedure was effective in 91% of cases as primary operations and in 100% in repeated operations. There were no life-threatening postoperative complications. In our opinion, meningitis in 4 cases is a conditional complication because these patients had several risk factors of this event (for example, intracranial entering of infected air, impaired immunity associated with multiple trauma, etc.). Transcranial approach is still advisable and relevant for repair of large and multiple skull base defects, as well as in case of failed previous endoscopic endonasal procedure.

Intraoperative endoluminal administration of sodium fluorescein 10% is a controversial issue in the literature. D. Clark et al. [12] reported 6 cases of endoscopic endonasal treatment of pneumocephalus and sodium fluorescein injection 30 min prior to surgery in order to visualize bone defect. A positive fluorescein test was observed in only one patient. In authors’ opinion, it was caused by low CSF pressure (fluorescein did not have time to reach CSF fistula). In this case, it is advisable to artificially increase CSF pressure by endoluminal injection of saline solution or Ringer—Locke’s solution. Composition of

![Treatment algorithm for pneumocephalus.](image)
the last solution is very similar to CSF. We emphasize that this drug is not certified for endolumbar administration.

We have developed treatment algorithm for pneumocephalus after analysis of our own experience and world literature data (Fig. 3).

**Conclusions**

1. Pneumocephalus should be suspected in a patient with cerebral and psychiatric symptoms and previous nasal liquorhea. Early diagnosis will be valuable to choose adequate treatment strategy. 2. Conservative therapy is indicated for confirmed pneumocephalus after previous acute injury or in early period after neurosurgery associated with dissection of meninges.

**REFERENCES**

Treatment of patients with pneumocephalus is a difficult problem. Craniocerebral and craniofacial injuries are the most common causes of pneumocephalus. In recent years, iatrogenic injury of skull base followed by tension pneumocephalus has become more frequent. The report of E. V. Shelesko et al. is highly relevant from this point of view.

A retrospective analysis included 30 patients with skull base defect followed by pneumocephalus. All patients were treated at the Burdenko Neurosurgery Center. Traumatic brain injury was the most common cause of pneumocephalus. Endoscopic endonasal repair of skull base defect was successful in more than 90% of cases. The authors analyzed their own results and literature data and formulated treatment algorithm for these patients. The research is of great interest for neurosurgeons and ENT surgeons.

A.M. Zaitsev (Moscow, Russia)
Postoperative Nausea and Vomiting in Neurosurgery: The Approaches are Varied but the Problem Remains Unsolved

M.I. KLYUKIN*, A.S. KULIKOV, A.YU. LUBNIN

Burdenko Neurosurgical Institute, Moscow, Russia

Postoperative nausea and vomiting (PONV) can induce brain displacement and herniation, especially in patients with cerebral edema.

Objective — to evaluate the urgency of the problem associated with postoperative nausea and vomiting in current clinical practice (with modern approaches being used for its prevention) and to reveal the risk factors of PONV that are typically encountered in neurosurgical patients.

Material and methods. A prospective observational study involved 240 patients who had undergone elective surgeries at the N.N. Burdenko National Scientific and Practical Center for Neurosurgery between July and November 2017. The data were collected from the questionnaires filled out by the patients during the first 48 h after the surgery and from patients’ medical records.

Results. The overall rate of PONV was 39.6%. Thirty-six out of 53 (68%) patients developed PONV after the posterior fossa surgeries. The risk of PONV in this group was significantly higher ($p<0.05$) compared to the rate of PONV after interventions at a different location. The rate of PONV after treatment of extracranial pathology was ~10.5%; for a different location, it was as high as 32—37%.

Intraoperative dexamethasone was used in 156 (65%) patients; in this group, the rate of PONV was 39.9%. Patients received ondansetron at a dose of 8 mg for a preventive purpose at the end of the surgery. A total of 162 patients were given the drug; 59 (36.4%) of them developed PONV during 48 h post-administration. Seventy-eight patients did not receive ondansetron. Thirty-six of them (46.2%) ($p>0.05$) developed PONV. The rate of PONV assessed during the first 8 h after surgery was 22.8% in patients who had received ondansetron and 37.2% in those who had not received it ($p<0.05$). Patients who had not intraoperatively received a combination of these drugs developed PONV in 55 (45%) cases ($p>0.05$).

Conclusion. The problem associated in PONV remains topical in neurosurgery. The current approaches are not absolutely effective for prevention of PONV, whose rate ranges between 10.5 and 68% depending on surgery location. Further studies focused on administration of NK-1 receptor antagonists and electrical stimulation of the median nerve are needed to enhance the effectiveness of PONV prevention.

Keywords: postoperative nausea and vomiting, risk factors, neurosurgery.

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Anesthesia in the same fashion was applied in the majority of adult patients including premedication with midazolam and tavegil in operating theatre, TIA with propofol, analgesia with fentanyl and miorelaxation with rocuronium. Regional analgesia of the scalp with ropivacaine was made in 15 patients. Postoperative analgesia was given using non-steroidal anti-inflammatory drugs (NSAIDs) (lornoxicam, ketonal) and tramadol in case of ineffective therapy (n=41). Fentanyl transdermal patch was applied in 5 patients.

Analysis of questionnaire survey data and medical records involved the following data: demographic characteristics, surgical and anesthetic features, Apfel score of risk factors (sex, smoking, previous PONV or seasickness, opioids administration in postoperative period), risk factors associated with surgery, anesthesia and other parameters, used prophylactic measures (dexamethasone and ondansetron) and PONV therapy. Severity of nausea and vomiting was assessed in accordance with 4-score scale within 48 hours after surgery: 0 score — no nausea, no vomiting, 1 score — nausea without vomiting, 2 scores — nausea and gagging, 3 scores — nausea and vomiting (Appendix 1).

Statistical analysis was carried out using Microsoft Excel 2007 and Statsoft Statistica 10 software packages. Mean±standard deviation was calculated. Statistical significance of between-group differences was assessed using Fisher’s exact test. Differences were significant at p<0.05. The local ethics committee approved this study.

**Results**

Twenty-eight patients were excluded from the study at the stage of data collection. Exclusion reasons: sensorimotor aphasia after surgery (n=2), prolonged postoperative ventilation (sedation) (n=9), incomplete personal data (language barrier, early discharge, refusal to answer the questions of the researcher, etc.) (n=17).

Final analysis included 240 questionnaires and medical records. Data on age, sex, body weight, physical status are summarized in Table 1.

<table>
<thead>
<tr>
<th>ASA class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (9.6)</td>
<td>145 (60.4)</td>
<td>66 (27.5)</td>
<td>6 (2.5)</td>
<td></td>
</tr>
</tbody>
</table>

Final analysis included 240 questionnaires and medical records. Data on age, sex, body weight, physical status are summarized in Table 1.

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Mean age 39±21 years (range 3 months — 79 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (18—79 years) — 186 (77.5%) Children (younger 18 years) — 54 (22.5%)</td>
</tr>
<tr>
<td>men 76 (40.9%) women 110 (59.1%) boys 37 (68.5%) girls 17 (31.5%)</td>
</tr>
<tr>
<td>139 patients aged 3 months — 50 years; 101 patients younger 3 years old and older 50 years</td>
</tr>
<tr>
<td>Body weight 66±26 kg</td>
</tr>
</tbody>
</table>

Table 2. Distribution of patients regarding severity and onset of PONV

<table>
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<tr>
<th>PONV severity</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>24</th>
<th>48</th>
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<tbody>
<tr>
<td>0 score</td>
<td>224</td>
<td>212</td>
<td>202</td>
<td>210</td>
<td>185</td>
<td>195</td>
<td>208</td>
</tr>
<tr>
<td>1 score</td>
<td>2</td>
<td>7</td>
<td>16</td>
<td>13</td>
<td>22</td>
<td>21</td>
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<tr>
<td>2 scores</td>
<td>1</td>
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<td>3</td>
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<tr>
<td>3 scores</td>
<td>13</td>
<td>14</td>
<td>21</td>
<td>14</td>
<td>30</td>
<td>21</td>
<td>8</td>
</tr>
</tbody>
</table>

Number of patients with PONV, n (%) 16 (6.6) 28 (11.7) 38 (15.8) 30 (12.5) 55 (22.9) 45 (18.8) 32 (13.3)
operative period resulted PONV in 51.2% of patients (34.5% without tramadol) \( p > 0.05 \).

The same scale was applied to analyze risk factors of PONV in children. We found higher risk of PONV in children aged 3 years and older compared with children under 3 years old \( (52.4\% \text{ vs. } 15\%; \ p < 0.05) \). PONV were also more common in case of previous PONV in a child or his relatives \( (89\% \text{ vs. } 22.2\%, \text{ respectively}; \ p < 0.05) \).

There were significant risk factors of PONV associated with anesthesia. TIA with propofol was used almost in all patients \( (96\%) \). Induction with sevoflurane was applied only in 9 children. PONV occurred in 4 cases. However, it was impossible to verify significant between-group differences due to small sample size. In addition, we assumed a higher incidence of PONV in patients who received large intraoperative doses of opioids. However, this assumption was not statistically confirmed. Fentanyl dosages over 5 \( \mu g/\text{kg/hour} \) were used in 41 patients. PONV occurred in 14 \( (34\%) \) of these patients. Lower dosages of fentanyl resulted PONV in 41\% of cases. The hypothesis about the effect of high intraoperative doses of fentanyl on the increase of early \( (\text{within } 4 \text{ h after extubation}) \) incidence of PONV was not confirmed too.

The use of dexamethasone and ondansetron is also measure to prevent PONV in our center in addition to TIA with propofol. Dexamethasone was intraoperatively administered in 156 \( (65\%) \) patients \( (50\% \text{ — at the beginning of surgery, } 50\% \text{ — at the end of procedure}) \). Intraoperative single dosage was 8 \( \mu g \) in most adults. A 48-hour incidence of PONV was 39.9\% \( (75 \text{ out of } 18 \text{ patients}) \) after single injection of dexamethasone.

Ondansetron was prophylactically administered at the end of the operation \( (8 \text{ mg or } 0.1 \text{ mg/kg}) \). This scheme was applied in 162 patients. PONV appeared in 59 \( (36.4\%) \) patients. In 78 cases, this drug was not administered and PONV occurred in 36 \( (46.2\%) \) cases \( (p < 0.05) \). The effectiveness of ondansetron was more clear within 8 hours after surgery. PONV was observed in 22.8\% of patients with administered ondansetron and in 37.2\% \( (p < 0.05) \) of patients who did not receive this drug. Intraoperative injection of dexamethasone and ondansetron was made in 118 \( (49.2\%) \) patients. Emetogenic reactions was observed in 40 \( (33.9\%) \) of them. On the contrary, PONV developed in 55 \( (45\%) \) patients without intraoperative administration of dexamethasone and ondansetron \( p > 0.05 \).

Discussion

Our results convincingly prove that the problem of PONV remains relevant in neuroanesthesiology despite significant progress in pharmacological prophylaxis. In our sample, PONV was observed in 42.1\% \( (93 \text{ out of } 221) \) of patients excluding extracranial interventions. This value is comparable with literature data \([3, 4]\).

Surgical area is the most important predictor of PONV in neurosurgery. According to our data, incidence
of PONV after subtentorial surgery is more than 2 times higher than that after other operations (68% versus 31.6%). These data are similar to the literature [5—6, 16—19].

Our results are in good agreement with international data on the effect of nonspecific risk factors on the incidence of PONV [1, 3]. Female gender, non-smoking status, postoperative use of opioids and previous PONV as the components of the Apfel prognostic system are still the most important risk factors of this complication. The same is true for neurosurgical patients [20, 21]. Age described in the literature [21, 22] is also significant factor. In our study, nausea and vomiting were less common in patients younger than 3 and older than 50 years.

In our opinion, the greatest incidence of PONV within 4—24 hours after extubation in our study may be associated with a time-limited effect of pharmacological prophylaxis because the drugs were administered only once. Ondansetron and dexamethasone administered during surgery with residual sedation after TIA prevented nausea and vomiting within 4 hours after operation. In the future, this effect is progressively reduced. Therefore, searching for the optimal time and approaches to prevention of PONV is relevant. Guidelines for the management of PONV (2014) mention 6-hour period between administration of anti-emetic drugs. Thus, any medicines may be used for correction of PONV in 6 hours after surgery and later including those previously used for prophylaxis [12].

We consider that demonstrated efficacy of drug-based prevention of PONV in general population of neurosurgical patients is a significant result of the study. We found a decrease of the incidence of emetogenic reactions by 15% within 8 hours and by 10% within 48 hours after surgery after injection of ondansetron. We emphasize that ondansetron and dexamethasone are mentioned in recent guidelines for the management of PONV (2014) [12] as recommended antiemetic agents with confirmed efficacy [8—11, 13—15]. Similar data are obtained in our study. Nevertheless, positive results of prevention achieved in recent years with the widespread use of dexamethasone (78% of patients) and ondansetron (68% of patients) did not result significant decrease of the incidence of PONV. This value is still high in neurosurgery (39.9 and 36.4% for dexamethasone and ondansetron, respectively). In this regard, it is relevant to search for new highly effective approaches to prevent and treat PONV. According to the world literature [23—29], certain methods including PONV prevention using droperidol, NK-1 receptor blockers and non-drug treatment (for example, median nerve stimulation) are analyzed.

Conclusion

Our research has shown that PONV is currently relevant problem in neurosurgery. Even propofol-based TIA with dexamethasone and ondansetron is not fully effective scheme to prevent PONV. Incidence of PONV is 10.5—68% depending on the area of intervention. In our opinion, further research is needed for more effective prevention of PONV with the inclusion of new drugs, such as NK-1 receptor blockers, as well as alternative methods, in particular stimulation of median nerve.

Authors’ participation:
Concept and design of the study — M.K., A.K.
Collection and analysis of data — M.K.
Statistical analysis — M.K., A.K.
Writing the text — M.K.
Editing — A.K., A.L.

Authors declare no conflict of interests.

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**Commentary**

The problem of postoperative nausea and vomiting (PONV) is particularly relevant for neurosurgery. High incidence of PONV is a typical feature of neurosurgical patients while early postoperative vomiting may be both a cause and a consequence of intracranial surgical complications. The article is devoted to a topical common issue for neurosurgery, neuroanesthesiology and neurological intensive care. The novelty of the work is determined by a low effectiveness of the “gold standard” for prevention of PONV (combination of ondansetron and dexamethasone). Thus, the authors emphasize advisability of searching for more effective methods for prevention of PONV and their widespread introduction into routine clinical practice. A prospective study design and standardized assessment of PONV make the results reliable. Actual references demonstrate comprehensive analysis of the problem and once again emphasize relevance of the study and significance of results. A clearly structured abstract reflects the essence of the work. The article is undoubtedly of interest for readers of the journal.

*K.A. Popugaev (Moscow, Russia)*
Appendix 1

PONV form

Name_________________________ phone number: _____________________
Medical record №_________ Age______ Sex ______ Hand_______
Height________Body weight________BMI________ ASA class ______ Department __________
Diagnosis:____________________
Surgery:____________________
Anesthesiologist ______________________Surgeon:__________________
Duration of anesthesia: from______to______ Date of operation:_____
ICU-stay: from______to______ Extubation time:_____

Apfel risk factors of PONV

- Female sex
- Non-smoking status
- Previous PONV or seasickness
- Postoperative use of opioids

Surgery-related risk factors:
1. Infratentorial intervention
   With:
   - removal of acoustic neuroma
   - microvascular decompression
2. Fat graft deployment for liquorrhea
3. Lumbar drainage insertion
4. Liquorrhea/pneumocephalus
5. Orbital surgery

Anesthesia-related risk factors
- Inhalation anesthetics
- Intraoperative arterial hypotension
- Use of neostigmine
- Total intraoperative dose of opioids

Other risk factors:
- Age under 50 years old
- Surgery time over 60 min
- Menstruation on the day of surgery
- Infracrani al hypertension
- Postoperative pain, VAS score ____, time of pain syndrome __________.
- Postoperative hypertension

Total risk factors:_________.

PONV prevention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time</th>
<th>Dose</th>
<th>OT/ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA/sedation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Methylprednisolone</td>
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<tr>
<td>Droperidol</td>
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<tr>
<td>Metoclopramide</td>
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<tr>
<td>Ondansetron</td>
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<td></td>
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</tr>
<tr>
<td>Infusion therapy</td>
<td></td>
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<tr>
<td>Regional Scalp Anesthesia</td>
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<tr>
<td>Anesthesia NSAIDs</td>
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<tr>
<td>Other</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dexametomidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine blockers</td>
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</tbody>
</table>
Assessment of PONV severity and sedation of patients

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>0 h</th>
<th>2 h</th>
<th>4 h</th>
<th>8 h</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

0 score — no nausea, no vomiting, 1 score — nausea without vomiting, 2 scores — nausea and gagging, 3 scores — nausea and vomiting, mild vomiting 1—2 times, moderate — up to 5 times, severe — more than 5 times.

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>0 h</th>
<th>2 h</th>
<th>4 h</th>
<th>8 h</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsay Sedation Score</td>
<td></td>
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</tbody>
</table>

Evaluation within 8 hours after anesthesia or later in case of sedation

**PONV therapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>OT/ICU</th>
<th>Dose, route, multiplicity, time</th>
</tr>
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<tbody>
<tr>
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</table>

Features and additions:
— vomiting from changing body position
— vomiting during extubation
The modern approach to the treatment of neurogenic tumors depends on localization and dimensions of tumor, potential risks of certain method. Treatment of sacral tumors is difficult due to the need for combined anterior-posterior approaches in most cases. These procedures are associated with a high risk of injury of the vessels, nerves or rectum wall intimately adjacent to the tumor capsule.

Neurogenic sacral tumors are extremely rare. So, T. Rasmussen et al. [1] found only 35 (7%) cases of neurogenic sacral tumor among 557 patients with spinal tumors. Database analysis confirmed that there is only one patient with neurogenic sacral tumor per 40,000 patients with spinal tumors. The majority of patients with neurogenic sacral tumors have neurofibromatosis [2].

As a rule, progression of the tumor results clinical manifestation. Possible symptom is isolated local or radicular pain. Dysfunction of pelvic organs is less common. Clinical symptoms always indicate progressive tumor growth, while malignancy should be suspected in case of large tumor [3—5]. Neurogenic tumors rarely infiltrate bone tissue. Even malignant transformation is often characterized by expansive local growth. Nevertheless, bone tissue destruction is common. Even small neurogenic tumors should be removed radically considering the possibility of malignant transformation [6].

Stereotactic radiotherapy is one of the treatment modes for neurogenic sacral tumors without significant symptoms [7—10].

Surgical approach to neurogenic sacral tumor is determined by localization and dimension of tumor, adjacent structures.

According to P. Klimo et al. [11], all neurogenic sacral tumors may be divided into 3 types (Fig. 1). The authors propose a certain approach for each type of tumor growth. Posterior approach is advisable for tumors type I, combined anteroposterior or only posterior approach — for tumors type II. Combined posteroanterior approach is required for tumors type III. This approach implies dissection and intersection of sacral nerve root as tumor growth source with subsequent foraminal dissection of its cuff to facilitate tumor dissection through anterior approach. After that, the tumor is removed through anterior retro- or transperitoneal approach.

We report the clinical case of removal of tumor type II. Radical resection was achieved by sacral amputation below S1 only through posterior approach.

Case report
A 23-year-old patient P. appealed to the Burdenko Neurosurgery Center in 2015 with complaints of severe local pain within the sacrum, perineum and impaired anogenital sensitivity. MRI/CT confirmed sacral tumor with a cystic component and S1—S5 bone destruction (Fig. 2). The diagnosis was questioned considering complex configuration of the tumor and bone tissue destruction. Therefore, diagnostic navigation-assisted percutaneous CT biopsy of the tumor was performed at the first stage.

Morphological diagnosis was neurinoma.

Considering dynamic MRI data (tumor enlargement) and the absence of severe neurological symptoms, radiotherapy instead of radical resection was preferred to preserve function of the pelvic organs. Stereotactic hypofractionated radiation therapy was made using CyberKnife (bremsstrahlung photon radiation from 6 MeV electrons). Tumor volume was 90 cm³, mean single focal dose — 5.2 Gy, mean focal dose — 26 Gy.

The follow-up period was 24 months. There was no significant neurological deficit within the follow-up period. Moreover, regression of pain syndrome was observed in 3 months after radiotherapy. However, the patient again noted local pain in 2017. Rectal bleeding not associated with hemorrhoids was also disturbing. No erosions, fissures, ulcerations or tumor penetration of the bowel wall were observed during sigmoidoscopy. At the
same time, bleeding could be an expected complication considering intake of large doses of non-steroidal anti-inflammatory drugs. Contrast-enhanced MRI/CT of the lumbosacral area confirmed continued tumor growth at the level of S1—S5 (Fig. 3).

Surgical treatment was offered. Radical removal of tumor with simultaneous lumbar-pelvic trans-S2-stabilization and perineal repair were scheduled considering previous radiotherapy and features of tumor growth. Stabilization was assumed due to possible postoperative stress fracture of residual sacrum and instability.

**Surgical stages**

Prone positioning of the patient was applied. Linear incision along spinous processes was performed slightly lateral to intergluteal fold (Fig. 4).

Sacrum was skeletonized, sacrum was destroyed within S2—S3 (Fig. 5).

Surgical procedure included S1-laminectomy S1, ligation of the roots below S2 entering into parenchyma of the tumor. Intact sacral tissue below S1 was sawn. Sacrotuberous and coccygeotuberous ligaments, piriformis muscles were transected. Presacral fascia was dissected from the rectal wall, nerves of sacral plexus were transected within the peripheral segment (Fig. 6).

Tumor and sacrum were removed en bloc. Transpedicular stabilization L5—S1, lumbar-pelvic stabilization through lateral sacral masses at the level of S2 were carried out (Fig. 7).

The last stage was perineal repair by suturing of free muscle flaps of the gluteal muscles. Skin was sewn using intradermal suture (Fig. 8).
The patient was activated on the 1st postoperative day. Drainage was applied within 5 days.

There are no MRI signs of tumor, serous cavity, perineal hernia or other complications (Fig. 9).

Urological rehabilitation including bladder stimulation, periodic catheterization, physical therapy, cholinomimetics intake was carried out during 3 months after surgery. Reduced volume of residual urine up to 20—50 ml, no episodes of urinary retention or incontinence and normal defecation were observed 3 months later. The only manifestation of discomfort was superficial hypesthesia within the anus.

Discussion and conclusions

There are various sacral tumors. These are primary bone tumors as a rule (chordoma, giant cell tumor). Neurogenic tumors is only small percentage of sacral neoplasms. At the same time, these tumors are usually characterized by aggressive growth and frequent malignant transformation [12—14]. Malignant transformation is more common for xanthomatous neurofibroma with long-term previous growth. A biopsy is not always highly informative because surgeon aims at the most massive part of the tumor and specimen does not always contain malignant tissue.

In our case report, surgical strategy was determined by complete sacral destruction at the level of S2—S5. Moreover, risk of malignant transformation was particularly significant considering previous radiotherapy and subsequent continued growth of the tumor.

There are literature data [9, 10] of secondary tumors or malignant transformation of benign tumors after conventional radiotherapy. Therefore, the majority of authors consider radiation therapy associated with high risk.

Nevertheless, modern practice confirms that radiosurgery or hypofractionated high-dose radiotherapy is an alternative to surgical treatment in patients with neurogenic spinal tumors [7, 8]. However, only clinical cases or small samples are analyzed in the majority of publications. Therefore, it is extremely difficult to predict the result of treatment. In our case report, there were MRI signs of tumor enlargement after radiotherapy associated with pain syndrome and risk of malignant transformation of the tumor. Considering these findings, surgical treatment was preferred.

Various aspects of surgical treatment are well described in the literature. J. Feldenzer et al. [15] operated 9 patients. Combined removal of the tumor through anteroposterior approach was applied in 2 cases, posterior approach was used in other patients. At the same time, 2 patients from the group of posterior approach had malignant tumors of the peripheral nerves and died within 3 years after treatment. There were no recurrences in other cases. J. Domínguez et al. [16] reported 6 patients with giant sacral schwannomas. Anteroposterior approach was used in 2 cases, posterior approach — in other patients. Recurrent tumor was observed in 3 patients with intradural spread of the neoplasm. It should be noted that 1 patient had recurrence in 17 years after surgery. C. Abernathey et al. [17] used posterior approach in 10 patients, anterior approach — in 3 patients. Four patients required removal of the intrathecal component of tumor. Total removal was noted in 4 cases. Nine patients after partial resection of tumor had no symptoms within the entire follow-up period. However, redo surgery was required in 4 (44%) cases. These patients had no signs of

Fig. 3. Continued growth of sacral tumor after stereotactic radiotherapy.

a — sagittal CT-scan of the lumbosacral area; b — CT-based 3D-image, median slice in sagittal plane; c — axial CT-scan of the sacrum.
continued growth or malignant transformation of the tumor within 7—84 months of the follow-up. Anterior additional approach was applied in 3 of these patients, combined anteroposterior approach — in 1 patient. One patient needed for additional pelvic stabilization, but the authors did not indicate the reasons for this procedure. Complications included pelvic organ dysfunction in 1 patient, anogenital sensory disturbances in 4 patients, motor disorders and movement problems in 1 patient. Wound complications were described in 3 patients.

There are no modern literature data regarding sacral amputation or total sacrectomy for potentially benign or potentially malignant sacral tumors because sacrectomy is preferred for locally aggressive or completely malignant sacral neoplasms (osseous tumors as a rule).

Partial resection of the tumor was not advisable and would result recurrent tumor in our case. Moreover, S3—S5 roots passed through the tumor parenchyma. So, en bloc resection was justified.

Interestingly, there was only transient dysfunction of pelvic organs in postoperative period. This was explained by bilateral preservation of S2 roots. According to the literature, intact S2 roots are essential for normal function of internal urethral sphincter. Normal defecation depends on various factors, in particular intact perineal function and normal sensitivity of filling and emptying rectal ampulla.

J. Wilfrid [18] uses data of O. Foerster et al. who described multiple variants of innervation of the pelvic organs in 1927. Therefore, pelvic reinnervation and positive outcomes of rehabilitation are possible and desirable (Table).

Sacroiliac joint instability is another important common problem complicating postoperative period. As a rule, instability occurs after resection of more than 50% of sacroiliac joint, on the background of osteoporosis or prolonged excessive load. This complication requires additional stabilization and restoration of pelvic ring integrity [19].

Considering all precautions and world experience, we completed the operation by lumbar-pelvic stabilization.
**Fig. 6. Intraoperative image.**

a — laminectomy is performed (tumor tissue is indicated by the arrow); b — sacral ligaments are dissected, the sacrum is raised to detach rectal wall from presacral fascia.

**Fig. 7. Intraoperative images.**

a — bed of excised tumor, free S2 roots are visualized (white arrows); b — deployed lumbar-pelvic stabilization system; c — perineal repair is made using polypropylene material, area of ligated roots is additionally covered with plastic material; d — sacrum and tumor removed en bloc in anteroposterior and lateral planes; e — intraoperative 3D-reconstruction of X-ray scans. View of stabilization system.
Fig. 8. Scheme of dissection of free flaps of major gluteal muscles (a, b) and healed wound (c).

Fig. 9. MRI of the lumbosacral spine in 3 planes in 2 months after surgery.
a — sagittal plane; b — frontal plane; c — axial plane.

Variants of pelvic organ innervation by O. Foerster et al. (1927)

<table>
<thead>
<tr>
<th>Pelvic organs</th>
<th>Variants of innervation</th>
<th>Variants of innervation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Th11—L2; S2—S4</td>
<td>Th11—L2/S2—S3</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Th10/Th11—Th12</td>
<td>Th11—Th12/L3</td>
</tr>
<tr>
<td>Prostate</td>
<td>Th10/Th11—L1</td>
<td>Th12—L3</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Th10/Th11—L1</td>
<td>Th12—L3</td>
</tr>
<tr>
<td>Uterus</td>
<td>Th10—L1/S2—S4</td>
<td>Th12—L3; S2—S3</td>
</tr>
<tr>
<td>Rectum</td>
<td>S2—S4</td>
<td>L1—L3; S2—S5</td>
</tr>
</tbody>
</table>
Conclusions

Radical resection of giant neurogenic sacral tumors may be followed by reduced incidence of local recurrence, prevents local malignant transformation and improves survival. En bloc resection is justified despite high risk of neurological, wound, intraoperative complications, as well as possible lumbar-pelvic destabilization. Restoration of lost quality of life after surgical trauma is one of the most important objectives of future researches devoted to rehabilitation of pelvic functions after various variants of sacrectomy.

Authors declare no conflict of interests.

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Received: 14.01.19

Commentary

The article is devoted to the one of the most difficult issues of modern spinal neurosurgery and neurosurgery as a whole. It is diagnosis and treatment of neurogenic sacral tumors. Diagnosis of these diseases is a difficult problem even for well-experienced specialist due to unclear clinical picture at the early stages of disease. The authors emphasize technical complexity and highly traumatic surgical treatment of sacral tumors due to close proximity of various vital structures (great vessels, nerves and pelvic organs). Successful surgical treatment of this rare disease, authors’ opinion and modern literature data are presented in the article. There are various unresolved issues due to insufficient scientific development of this problem. Therefore, further researches are required, while this report is a contribution to the development of this important problem.

A.O. Gushcha (Moscow, Russia)
The problem of degenerative-dystrophic spinal changes is still relevant. Complaints of pain and discomfort in cervical spine are still often found in employable people as the second common complaint after lumbar pain. Clinical and instrumental examination reveals degenerative-dystrophic changes in cervical spine within 1—2 segments (rarely 3—4 levels) in the majority of patients with neurological symptoms.

Surgical treatment of local stenosis affecting one vertebral segment is well-developed including surgical approach, decompression and spinal fusion with autologous or allografts, interbody cages and imposition of dynamic plates [1 —3]. Stand-alone cage is currently the most acceptable variant of spinal fusion surgery. This method is used for both mono- and polysegmental lesion.

However, multilevel lesion narrows the choice of decompression and spinal fusion methods and causes discussions among professionals.

Researchers emphasized the need and importance of reconstruction and strengthening of anterior support column in the early twentieth century. So, H. Ito et al. [4] published the work “New Radical Surgery for Pott's Disease” in 1934. The authors described the technique of strengthening and replacement of vertebral bodies by a tibial autograft. Researchers had searched for the most suitable material for spinal fusion surgery since that time. As a rule, these were modifications of rib grafts, iliac crest autografts and grafts from femur and tibia. All these grafts were used for extended corpectomy. Along with a large number of autograft modifications, high incidence of postoperative complications including pseudoarthrosis (over 20%) and fractures of autografts was also observed [5, 6]. In the 1980s, J. Kostuik [7] and K. Kaneda et al. [8] reported the use of systems with metal rods and plates to retain osseous graft and accelerate interbody fusion. Titanium mesh cages have been widely used as interbody implants since 1986. Simple design allowed intraoperative selection of the implant with necessary height, while its filling with osteoconductive material improved quality of interbody fusion. This method of interbody fusion gained trust and proved to be affordable and reliable for mono- and polysegmental cervical disc- and corpectomy [9].

Currently, zero-profile stand-alone cages are becoming more and more popular. These cages are usually made from polyetheretherketone (PEEK). It is a polymer resistant to high temperatures, vapor and radiation and characterized by increased wear resistance. PEEK is similar to bone tissue due to above-mentioned biomechanical properties combined with high strength and resistance to dynamic effects. Therefore, this material is favorable for spinal fusion procedures.

Constructive feature of cages is their possible fixation with monocortical screws in the bodies of overlying and underlying vertebrae with subsequent dense stabilization of anterior support column. Therefore, there is no need for surgeon to fix operated vertebral segment (plate installation). Moreover, surgical trauma and time of procedure are significantly reduced. Minimal trauma of anterior longitudinal ligament combined with zero-profile implant is aimed at reducing degenerative changes in adjacent levels.

Case report

Patient M. appealed to the clinic with complaints of pain and numbness of the 1st—3rd fingers of both hands, permanent discomfort in cervical spine, dizziness and distraction. For the first time, the patient noticed pain and numbness in fingers in 2008 and appealed for medical help at the place of residence. MRI of cervical spine revealed...
revealed C4—C5 disc hernia. The recommended conservative treatment resulted temporary positive effect. Repeated MRI was performed in 2010 due to clinical deterioration. Progressive degenerative-dystrophic changes in C3—C4, C4—C5, C5—C6 discs were revealed. Conservative therapy with a mild positive effect was carried out in 2010—2017. In early 2017, the patient appealed for medical care again due to clinical deterioration including severe pain and numbness of the 1st—3rd fingers of both hands, discomfort in cervical spine, dizziness, confusion, inability to stay upright. A repeated MRI of cervical spine revealed severe degenerative-dystrophic changes, osteochondrosis and deforming spondylosis of cervical and upper thoracic spine with C3—C4, C4—C5, C5—C6, C6—C7 discs hernias. Physical examination: hypersthenic body type, excess fat deposition, BMI 37 (obesity grade II). Neurological examination: intact cranial nerves, no paresis, tendon reflexes are normal. Right-sided carpal tunnel symptom. Hypoesthesia within the dermatomes C3, C4, C5, C6. Coordination and Romberg tests are normal.

Thus, the following diagnosis was confirmed by complaints, anamnesis, clinical and instrumental survey: spinal canal stenosis, hernias of C3 — C4, C4 — C5, C5 — C6, C6 — C7 discs. Secondary radicular syndrome (Fig. 1).
Surgical treatment included total discectomy C3—C4, C4—C5, C5—C6, C6—C7, decompression, anterior cervical spinal fusion C3—C4, C4—C5, C5—C6, C6—C7 with cages Zero-P VA Lordotic (Synthes) filled with osteoconductive paste. Surgery was performed under general anesthesia. Patient positioning resulted in overextension of the cervical spine. Level of surgical intervention was determined using intraoperative electronic optical transducer (Fig. 2). An incision was made along the transverse skin of the cervical skin fold up to 5 cm long.

Further stages were tissue dissection, retractor deployment, and exposition of the anterior vertebral surface. It is noteworthy that dissection of the anterior longitudinal ligament from the surface of adjacent vertebrae was not required at this stage. This aspect minimizes subsequent degenerative changes in intact vertebrae. Separation of the anterior longitudinal ligament was required only at the level of targeted intervertebral disk due to design features of the cage. Next, C3—C4, C4—C5, C5—C6, C6—C7 discectomy was performed with evacuation of up to 50% of their contents. Further, interbody distractor was installed, remnants of intervertebral discs, hernias, and marginal bone growths were removed. Vertebral endplates were cleaned to reduce the risk of spinal fusion failure.

We used zero-profile PEEK cages with blocking mechanism in combination with osteoconductive paste based on hydroxyapatite and β-tricalcium phosphate for spinal fusion surgery. Measurement of interbody space using templates was followed by selection of appropriate cage, its filling with osteoconductive paste and deployment into the required level. At the final stage, cage was fixed into overlying and underlying vertebrae with monocortical screws under intraoperative x-ray control. After that, the wound was closed with insertion of latex drainage.

The patient was activated the next day after surgery and complained of mild pain within the postoperative wound. No neurological symptoms were observed. Control X-ray examination confirmed a recovery of the height of discs and cervical lordosis (Fig. 3). Postoperative period was uneventful. The patient was discharged in 4 days after surgery. Control MRI of the cervical spine in 1 month after surgery confirmed no compression of spinal cord and spinal roots. No dislocations of implanted cages were found. There was a focal myelopathy at the C3—C4 level. This lesion was not diagnosed prior to surgery due to degenerative-dystrophic changes followed by severe spinal canal stenosis (Fig. 4). The patient was referred to specialized institution for further rehabilitation.

Fig. 3. Postoperative X-ray scans of the patient K. (explanations in the text).
Discussion

To date, two techniques have become the most popular for spinal fusion surgery and vertebral-motor segments fixation: 1) interbody cages with additional fixation with a dynamic plate; 2) zero profile stand-alone PEEK cages. Y. Chen et al. [10] reported similar results of both methods in patients with triple-level spinal lesion. Various authors [11, 12] argue that there are no significant differences between stand-alone cages and fixation with a dynamic plate. Postoperative decrease of segmental height is comparable after deployment of stand-alone cages and cages combined with dynamic plates and ranges from 14 to 18% [13, 14].

Obviously, dynamic plates result more equitable distribution of the load on interbody allo- or autograft due to certain design features. Therefore, this technique favorably influences formation of spondylodesis. However, it is also obvious that dynamic plate implantation is associated with a great number of complications. Migration of various components of fixation system (plate, screw, interbody implant) occurs in 10—16.5% of cases. Interbody fusion is absent in 15.8% of cases, significant degenerative-dystrophic progression in adjacent segments — in 40.5%, dysphagia — in 1—6.5%, heterotopic ossification of paravertebral tissues — in 21.5% of cases [15]. All above-mentioned complications require redo surgery as a rule [16]. The main causes of these complications are considered to be excessively reduced vertical dimension of stabilized vertebral segments and segmental straightening cervical sagittal contour without taking into account some structural and functional features of the biomechanical system “cervical vertebral motor segment — implants”. Another cause is plate-associated injury of anterior longitudinal ligament.

According to literature data, deployment of zero profile stand-alone interbody implants is followed by the smallest number of intra- and postoperative complications. Design features of these implants are essential in these outcomes. Italian authors [17] reported only 2 cases of cage migration among 85 patients including 29 cases of single-level lesion and 56 patients with a lesion of 2—4 segments. In 1 case, migration occurred in a patient with osteoporosis and long-term steroid therapy for renal failure. Numerous studies found mean incidence of spinal fusion of 91—97.1% [17—19], incidence of postoperative dysphagia — 9.0—16.3% [15, 20], degeneration of adjacent vertebrae — 3.3—9.8% [20, 21].

Above-described values clearly confirm the advantages of zero profile stand-alone cages over alternative methods.

Conclusion

As mentioned above, modern authors consider several methods of decompression and spinal fusion surgery for extended stenosis of cervical spinal canal. However, it is natural that procedures ensuring fast recovery of normal quality of life and minimal surgical trauma should be preferred.

There are some undoubted advantages of the technique described in the article:

— minimal surgical trauma (with radical correction of all disorders);
— minimal influence on the surrounding tissues, especially anterior longitudinal ligament, followed by reduced likelihood of degenerative changes in adjacent vertebral segments;
— the most favorable conditions for adjacent vertebrae fusion;
— fewer number of postoperative complications (migration of fixation system components, pseudoarthrosis, postoperative dysphagia);
— recovery of the quality of life as soon as possible;
— maximum cosmetic effect with a transverse incision in cervical fold.

Thus, above-described surgical approach should be preferred for extended stenosis of cervical spinal canal. This finding is confirmed by our and international data.

REFERENCES


Authors’ participation:
Concept and design of the study — K.M.
Collection and analysis of material — B.V.
Statistical analysis — K.M., B.V.
Writing the text — K.M., B.V.
Editing — K.M.

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Commentary

The article is a brief review of surgical approaches for degenerative cervical spine stenosis. Further, clinical example of a patient with degenerative stenosis at the C3, C4, C5, C6, C7 levels undergoing implantation of ZeroP Lordotic cages is reported. Perhaps, it is not entirely correct to indicate in name of the manufacturer of fixation system.

A.G. Nazarenko (Moscow, Russia)
Modern Aspects of Reconstructive Surgery of Skull Defects

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The aim of this study is to systematize the modern methods used for reconstruction of extensive and complex skull defects. Special attention is paid to computer technologies, including 3D imaging and CAD/CAM. Laser-based stereolithography is thoroughly reviewed among other additive technologies. We present our view of the problem associated with proper timing of cranioplasty and choice of materials for it. Complications of skull defect reconstruction are also discussed.

Keywords: reconstructive neurosurgery, skull defects, 3D image, CAD/CAM, laser-based stereolithography, molds.

Reconstructions of skull defects are ones of the oldest operations, that is confirmed by archaeological findings [1, 2]. Meanwhile, the problem of skull integrity reconstruction after depressed fractures, gunshot wounds and other lesions is still relevant [3—6]. The number of patients with cranial defects is constantly increasing due great incidence of traumatic brain injuries (TBI) and their consequences, extended indications for decompression craniotomy in patients with refractory intracranial hypertension, tumors of cranial bones and cerebrovascular diseases [7, 8].

Skull defects account over 30% among all clinical consequences of TBI requiring surgical treatment [9—11]. Reconstruction of skull defects is followed by cerebral protection against external factors, primarily permanent effect of atmospheric pressure. Therefore, syndrome of the trephined is prevented [12—14]. Normalized parameters of cerebral hemodynamics and cerebrospinal fluid circulation result improved neurological and cognitive functions [15—18]. Reconstruction of cosmetically significant defects contributes to social adaptation of patients. Thus, cranioplasty should be considered as a necessary aspect of rehabilitation in patients with TBI-associated skull defects [14—20].

In recent years, various aspects of skull defect reconstruction are of great interest including optimization of terms of surgical intervention, searching for new plastic materials and development of various repair techniques including intraoperative implant manufacturing [21—26].

1. Dates of skull integrity repair

Dates of skull integrity repair are still under discussion [27—29]. Some authors of retrospective trials [30—32] emphasized that time interval between bone fragments removal and skull defect repair does not influence risk of infection and overall outcome. Currently, there are no dogmatic indications regarding the dates of cranioplasty [33]. Some authors [34—36] consider early cranioplasty (<90 days) as preferable over late procedure (>90 days) due to reduced risk of complications after decompressive craniotomy, improved cerebral blood flow and metabolism (especially within the defect). Another advantage of early cranioplasty is prevention of “sunking skin flap” syndrome [27—29, 36]. However, delayed reconstruction is advisable in the case of local infection, concomitant inflammatory complications and local tissue changes near the defect [37, 38].

Literature data and our own experience also confirm the need for individual approach regarding dates of skull reconstruction [39, 40].

2. Plastic materials in skull defect repair

Development of modern biocompatible natural and synthetic plastic materials (PM) facilitate development of reconstructive neurosurgery. Characteristics of ideal material should be extremely similar to native tissues. Therefore, fresh autologous bone is still the “gold standard”.

Neurosurgeons often preserve autologous bone during decompressive trepanation in subcutaneous space of the anterior abdominal wall. Cryopreservation (−17, −80°C) and antiseptic solutions are also used. Autologous bone reimplantation reduces the risk of autoimmune reactions. This material is optimal skeleton for bone tissue and vascular growth. Moreover, this approach reduces the cost of the treatment. However, there is a high risk of infection (>10%) due to bacterial contamination despite these advantages [28, 30, 41, 42]. Another common complication is resorption of autologous bone (25—50% of cases) [4, 28, 29, 43]. Risk factors of this event are fragmented flaps, young age (<30 years), need for bypass, skull defect area over 120 cm² [44, 45]. Significant limitations for the use of autologous bone are

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Characteristics of cranioplastic materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous bone</td>
<td>Good establishment, low cost, strength, ability of osteoinduction</td>
<td>Resorption, risk of infection</td>
</tr>
<tr>
<td>Polymethyl methacrylate</td>
<td>Dense, inert, low cost, easy to use</td>
<td>Risk of infection, fragility, exothermic reaction</td>
</tr>
<tr>
<td>Hydroxyapatite</td>
<td>Mineral composition is comparable with a bone, good cosmetic result, local effects of osteointegration</td>
<td>Risk of infection, fragility (possible fractures), difficult intraoperative preparation</td>
</tr>
<tr>
<td>Titanium</td>
<td>Less susceptible to infection, not susceptible to corrosion, durable, good cosmetic result</td>
<td>Expensive, artifacts during neuroimaging, reduced elasticity in large defects, thermoconductive effect</td>
</tr>
<tr>
<td>Polyetheretherketone</td>
<td>Radiolucent, chemically inert, elastic, durable, convenient to use</td>
<td>Risk of infection, high cost, difficult combination with other plastic materials</td>
</tr>
</tbody>
</table>

insufficient amount of plastic material and advanced skull defects [5, 6, 46].

There are various requirements to modern plastic materials for skull repair: biocompatibility, available and easy modeling of implants of any shape and dimensions, shape retention, resistance to heat and cold, plasticity, minimal risk of infectious complications and, finally, an acceptable cost [47—51].

The use of alloplastic and titanium implants in reconstructive surgery of skull defects is reported in some articles [48—51]. There are the following stages in their manufacturing and improvement:

— bioinert (first generation) implants do not support the processes of osteosynthesis; no contact between the implant and the bone (development of fibrous capsule); — bioactive (second generation) implants are able for bone conduction and integration;
— osteoinductive (third generation) — promote bone regeneration (the future of cranioplasty).

Polymethyl methacrylate (PMMA), medical titanium, porous high-density polyethylene, hydroxyapatite, polyetheretherketone and others are the most common alloplastic implants. Experience of the use of these implants is described in the literature [47—52]. Advantages and disadvantages are summarized in the Table.

Modern techniques of reconstructive surgery with computer technologies allow making implants with necessary configuration and dimension for skull defect repair in a particular patient. Almost any biocompatible PM may be used for these purposes [53, 54].

High incidence of infectious complications in case of the contact of modern alloplastic materials with frontal sinus and nasal cavity makes it difficult to use these grafts for certain injuries, for example, cranio-orbital-facial defects. Titanium implants is exception. Combined application of autologous bone and alloplastic materials was developed to overcome this limitation. This method is able to isolate and distance the implant from superior paranasal sinuses and airways. Therefore, risk of infection is reduced [51, 54, 55].

Modern researches are devoted to searching and development of new generations of cranioplastic materials, improving the accuracy of manufacturing of the implants and reducing their cost.

### 3. 3D imaging and computed tomography in reconstructive neurosurgery

3D imaging was used in medicine even before the advent of X-ray computed tomography scanner. Wax 3D models of human tissues and organs were used to study human anatomy and pathology [56].

In the 1970s, J. Mazziotta and V. Hamilton [57] reported 3D reconstruction of neuronal structures using computer analysis of 2D images of histological slices. Tissue slices were obtained using light or electron microscopy. P. Teisser [58] was first who described 3D modeling of anatomical structures using axial computed tomography (CT) for correction of congenital and acquired craniofacial deformities. Certain skepticism of specialists was caused by low resolution of CT at that time and imperfect software. Further development of neuroimaging improved the accuracy of reproduction of various cranial and cerebral structures and 3D modeling. These models became widely available and reliable for diagnosis and preoperative planning. Preoperative 3D visualization of skull structures, true dimensions of deformations and defects and configuration features resulted more successful reconstructive interventions and objective assessment of their results [59—61].

At the Burdenko Neurosurgery Center 3D CT modeling has been used since the 1990s in patients with craniobasal and craniofacial lesions for assessment of skull defects and deformities and selection of optimal surgical approach [62—64].

Currently, computer technologies in 3D CT and MRI modeling are useful to obtain images of craniocerebral neoplasms and cerebral vessels, analyze and manipulate these images, perform virtual surgical interventions [65].

New generation of spiral CT scanners and their widespread introduction into clinical practice significantly extended application of this advanced technology in reconstructive surgery of skull defects (Fig. 1).
4. 3D modeling of the implant using computer aided design and manufacturing (CAD/CAM)

Precise anatomical recovery is particularly important in case of extensive and geometrically complex skull and craniofacial defects because it significantly affects cosmetic outcome and social adaptation of the patient. Manual intraoperative manufacturing of complex implants limits the choice of plastic materials, reduces expected cosmetic result, and increases duration of surgery and anesthesia. K. Shibahashi et al. [66] analyzed a large sample of patients within 10 years. The authors observed correlation of local postoperative infectious complications (12.3%) with duration of surgery.

The technique of preoperative implant manufacturing using CT data and subsequent CAD/SAM technologies were developed in 1996 at the University of Illinois, USA [67—69]. The essence of the technique is creation of an implant design using processing and segmentation of CT data with special programs (computer-aided design, CAD). The second stage is computer-aided manufacturing (CAM) of the implant using 3D model (3D printing) [70, 71]. Individually manufactured implants by CAD/CAM technology have undoubted advantages: high accuracy and durability, reduced surgical trauma and time of surgery and ultimately predictable stable functional and cosmetic results [72, 73]. However, high cost of these implants and need for redo surgery with removal of the implants and increased expenditures in case of any complications should be considered [74, 75].

Laser stereolithography is one of the common methods of CAD/CAM technology and actively used in reconstructive surgery of skull defects and maxillofacial surgery.

5. Skull defect reconstruction using laser stereolithography

Until the mid-1980s, technologies of 3D manufacturing in accordance with 3D model were based on subtraction (removal) of material by turning, milling, EDM or changing the shape of the model (forging, stamping, pressing). Machines with digital control were used for this purpose.

In the 1980s, additive technologies implying gradual augmentation (adding) of the material or change the matter phase state in a certain spatial area were actively developed. In 1986, C. Hull [76] patented a device for stereolithographic manufacturing a precise 3D acrylic objects based on their computer model. The technology implied layer-by-layer build-up of a liquid photopolymer composition hardening under laser beam.

Direct conversion of computer models into physical object was called as "rapid prototyping". Other names of this method are desktop manufacturing, 3D-printing, plotter. Currently, there are over 20 types of industrial
machines based on additive technologies. The main technologies of additive manufacturing are laser stereolithography, selective laser sintering, direct laser sintering of metal, selective laser melting, etc. [76—80].

Laser stereolithography was originally developed for aerospace and automotive industries. However, this method has attracted great interest in medicine, especially in reconstructive cranial surgery. The results of stereolithographic modeling (STLM) of the skull (3D-bi model) in craniofacial surgery were first shown by T. Lambrecht et al. [81] in 1987, N. Mankovich et al. [82] in 1990. H. Sailer et al. [83] used STLM for diagnosis and preoperative planning in patients with congenital craniofacial deformities and posttraumatic skull defects and noted its significant superiority in comparison with traditional diagnostic methods. In authors’ opinion, the most attractive aspect of STLM is available preoperative and intraoperative using an accurate physical skull model for assessment of dimensions and shape of deformity or defect. Moreover, 3D models are useful to assess the quality of bone tissue, determine the boundaries of osteotomy and resection of fibrous dysplasia. STLM database for patients with rare craniofacial deformities may be used for scientific and educational purposes.

J. Bill et al. [84] successfully used STLM for reconstruction of complex cranial defect after meningioma removal and purulent complication. The authors noted exact congruence of the implant with the edges of the defect and excellent functional and cosmetic results.

In Russia, STLM was first used in the early 2000s in patients with skull and facial defects and deformities [85—88]. There were over 500 successful reconstructive interventions for extensive and complex skull defects using this method for the last 20 years in the Burdenko Neurosurgery Center.

5.1. Intraoperative implant manufacturing

One of the advantages of stereolithography is obtaining not only skull model, but also the molds with configuration of the defect. These molds may be used for intraoperative or preoperative manufacturing of the implant with subsequent sterilization [85, 86, 89, 90].
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P. d’Urso et al. [91] used stereolithographic biomodels and molds for preoperative planning of the acrylic implants in 30 patients with cranial vault defects. Gas sterilization and autoclaving were applied. High accuracy of the implants was intraoperatively confirmed. The authors reported reduced time of intervention and excellent cosmetic results. This technique of implant manufacturing is recognized as cost-effective. S. Agner et al. [92] reported similar findings with minimal invasiveness of skull defect reconstruction and reduced hospital stay.

E. Tan et al. [93] described PMMA implant manufacturing from a mold for cranial vault defect reconstruction. Surgical outcome was estimated considering cranial symmetry index. This value was 96.2%. This technique has significantly reduced the cost of 3D-biomodels and individual implants.

It should be noted that the use of molds requires certain experience due to extremely changeable fluidity and plasticity of polymeric materials. Conventional surgery for skull defects is characterized by significant limitations in the implementation of spatial anatomical relationships, especially in complex areas such as parabasal, basal and craniofacial defects. Defects in these areas may be quite different. These defects are characterized by complex shape with uneven edges and often spread towards skull base. The molds provide the best anatomical assessment of the defect on the originally manufactured model in these cases. This is followed by creation of the implant congruent to anatomical curvature of the defect [94—96].

Stereolithographic models of skull and their molds have been used for the last 20 years in the Burdenko Neurosurgery Center. There is advanced experience in successful reconstructions of extensive and complex skull defects using molds from photopolymerizable solutions [97, 98]. Certain features were also revealed during this research. For example, fragile photopolymer material is associated with high probability of breakage and deformation during implant manufacturing (Fig. 2).

It should be noted that stereolithographic molds for skull defect modeling do not withstand long-term storage and re-sterilization due to changes of their spatial parameters.

5.2. Implant manufacturing using the molds from ultrahigh-molecular-weight polyethylene

Searching for more reliable methods of intraoperative implant manufacturing in reconstructive neurosurgery of skull defects led to the use of molds from ultrahigh-molecular-weight polyethylene [99—101]. There are certain advantages of this material:

— strength, stability under any strain efforts including mechanical pressing [102];
— inertness, no need to use separation materials;
— approved application in medicine;
— precise and convenient manufacturing of implants of various complexity.

Conclusion

Modern methods of reconstructive interventions using computer modeling and 3D-technologies of rapid prototyping changed skull defect surgery.

Improved quality of intraoperative implant manufacturing and the use of new press-molds resulted more reliable results of reconstruction of complex and extensive skull defects.

Searching and development of new technologies and methods of cranioplasty are currently ongoing simultaneously with significant progress in reconstructive neurosurgery.

Authors declare no conflict of interests.
Commentary

The article is devoted to modern aspects of reconstructive neurosurgery for skull defects. The problem is absolutely relevant because skull defects account over 30% of all consequences of TBI requiring surgical treatment. This problem has been discussed for a long time. However, the emergence of new technologies and materials requires their systematization and analysis in order to determine optimal surgical strategy in these patients.

Various synthetic materials have recently appeared which are effective for closure of post-craniotherapy or post-traumatic skull defect using 3D-technology. The authors comprehensively analyzed modern techniques of skull repair using their own experience and literature data. They systematized various biocompatible materials and emphasized their advantages and disadvantages that is very important. It is indisputable that these procedures are followed by favorable cosmetic outcomes, better rehabilitation and reduced duration of rehabilitation in case of neurological deficit.

The authors rightly emphasized that there are still no clear criteria for selection of certain type of material. There are also no clear recommendations regarding the dates of reconstructive surgery. This report is valuable to resolve above-mentioned problems to a certain extent. Moreover, the review is of undoubted interest for neurosurgeons, specialists for radiological diagnosis, neurologists, maxillofacial and plastic surgeons.

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Commentary

The problem of skull integrity repair is becoming increasingly important. First of all, this is due to wide spread of extensive decompressive craniotomy for TBI-associated uncontrolled intracranial hypertension and cerebrovascular accidents. This review is devoted to new opportunities in reconstructive neurosurgery. Predominantly, new digital technologies of recent decades are being considered. These methods radically changed the quality of cranioplasty in patients with skull defects. Particular attention is paid to intraoperative manufacturing of the implant congruent to the skull defect. Various manufacturing techniques from manual modeling to press-molds are constantly being improved. However, these methods still not sufficiently meet modern requirements. The authors describe manufacturing of press-molds from ultra-high-molecular-weight polyethylene in reconstructive neurosurgery. This is one of the promising directions for intraoperative implant manufacturing in skull defect repair. The reader will find valuable information about stereolithography and CAD/CAM technology in the review. These data will make it possible to get a complete picture of modern techniques of reconstructive neurosurgery and to be better oriented in choosing plastic materials. Undoubtedly, these findings will contribute to improvement of practical activity in reconstructive neurosurgery.

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