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Medulloblastoma in Children under Age of Three Years: Pathological Features and Clinical Management

M.V. RYZHOVA1*, O.G. ZHELUDKOVA2, E.V. KUMIROVA3, L.V. SHISHKINA1, T.N. PANINA1, S.K. GORELYSHEV1, E.A. KHUKHLAEVA1, N.A. MAZERKINA1, K.B. MATUEV1, O.A. MEDVEDEVA1, E.M. TARASOVA1, B.V. KHOLODOV1, O.YU. KAPELTULSKAYA1

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We present a series of 51 medulloblastoma tumors in children under three years of age collected at the N.N. Burdenko Neurosurgical Institute during the period between 2000 and 2010. 57% of the tumors showed desmoplastic/nodular histology. Fluorescence in situ hybridization (FISH) analysis detected amplification of the MYC oncogene in 4%, the MYCN oncogene – in 8%, and isochromosome 17q – in 16% of cases. 9q deletion was found in 8% of desmoplastic/nodular medulloblastomas. The results obtained demonstrate that desmoplastic/nodular medulloblastoma has a positive predictive value for progression-free survival. Another feature of the biology of medulloblastomas in children younger than three years is the lack of nuclear accumulation of β-catenin and 6q deletion. Medulloblastomas with MYCN oncogene amplification are often characterized by desmoplastic/nodular histology and a relatively favorable outcome. The most unfavorable prognostic marker is the MYC oncogene amplification, which was combined with the large cell/anaplastic medulloblastoma and isochromosome 17q in 100% of cases in our series; such tumors should be included in the high risk protocol.

Keywords: medulloblastoma, infants, copy number aberrations.

According to modern concepts, the term “medulloblastoma” is used for the heterogeneous group of diseases characterized by clinical, histological, and molecular features in patients of different ages [3, 11, 12, 14, 21–23, 31]. Tumors in children younger than 3 years of age are classified into a special group because of the limitation of radiation therapy in this case [2, 10].

51 cases of primary medulloblastoma were diagnosed in children younger than 3 years of age at the Department of Pathologic Anatomy, N.N. Burdenko Neurosurgical Institute, during the period between 2000 and 2010. The number of cases increased annually: from 1 in 2000 to 14 medulloblastomas operated on in 2010, which can most likely be attributed to the improved early diagnostics of these tumors by pediatricians at outpatient clinics, to upgrading of neurosurgical equipment, and to professional development of neurosurgeons [1]. The first symptom of the disease (due to the age of patients) was a loss of previously acquired skills. Hydrocephalus symptoms were also observed frequently; the average time interval between the first symptoms of the disease and diagnosis was 2–3 months. In over half of cases, the tumor developed in children aged 2–3 years old; boys were affected more frequently.

Materials and Methods

The clinical characteristics of patients are presented in Table 1.

An immunohistochemical assay with Anti-BAF47 BD antibody (Transduction Laboratories, clone 25/BAF47) at a 1:200 dilution was conducted in all cases in order to eliminate the atypical teratoid rhabdoid tumor. An immunohistochemical assay with Anti-β-catenin (BD Transduction Laboratories) at a 1:100 dilution was also conducted. Fluorescence in situ hybridization was carried out to study the possible copy number aberrations using the following commercial probes from Vysis (Abbott Molecular, USA): Vysis LSI MYC Dual Color Break Apart Rearrangement Probe, Vysis LSI N-MYC (2p24) Spectrum Green/CEP 2 Spectrum Orange Probe, Vysis Miller-Dieker Region/Isolated Lissencephaly Probe LSI LISI1 Spectrum Orange/LSI RARA Spectrum Green, Vysis LSI MYB Spectrum Aqua Probe, Vysis LSI BCR/ABL + 9q34 Tricolor, Dual Fusion Translocation Probe.

The data on belonging to a certain molecular subtype (subtypes SHH*, WNT**, C, and D [31]), which were determined by immunohistochemistry with four antibodies [23], were kindly provided by Prof. A.G. Korshunov (Department of Neuropathology, University of Hei-

*SHH – Sonic Hedgehog. The term “Sonic Hedgehog” is a joke from molecular geneticists: the molecular cascade was named after the computer game character.

**WNT – a combination of Wg (wingless) and Int. The Drosophila wingless gene had originally been identified as a recessive mutation suppressing wing development in the fruit fly. The homologous vertebrate gene Int1 (Integration 1) was first studied due to its presence near several integration sites of mouse mammary tumor virus.

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Results

Desmoplastic/nodular medulloblastoma (Fig. 1) recorded in 24 (57%) of children was the predominant histological variant in the 0–3 years age group.

We have also detected 5 cases of medulloblastoma with extensive nodularity (Fig. 2), which occurred exclusively in the 0–3 years age group.

Classical medulloblastoma (Fig. 3) was the second most frequent type after the desmoplastic/nodular type and was observed in 15 (29%) children. In 7 (14%) cases, medulloblastoma exhibited large cell/anaplastic histology (Fig. 4).

The fluorescence in situ hybridization has revealed two MYC oncogene amplifications (Fig. 5), MYCN oncogene amplification (Fig. 6) in 4 patients, and isochromosome 17q (Fig. 7) in 8 patients. A 9q deletion (Fig. 8) was also observed in four patients with desmoplastic/nodular medulloblastoma.

Table 1. Clinical characteristics of medulloblastoma patients younger than 3 years of age

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number of patients (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs.</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>1–12 months</td>
<td>5</td>
</tr>
<tr>
<td>13–24 months</td>
<td>12</td>
</tr>
<tr>
<td>25–36 months</td>
<td>34</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>32</td>
</tr>
<tr>
<td>female</td>
<td>19</td>
</tr>
<tr>
<td>Tumor localization:</td>
<td></td>
</tr>
<tr>
<td>medial</td>
<td>36</td>
</tr>
<tr>
<td>lateral</td>
<td>4</td>
</tr>
<tr>
<td>medial and lateral</td>
<td>11</td>
</tr>
<tr>
<td>Metastatic disease at the moment of diagnosis:</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>26</td>
</tr>
<tr>
<td>M1–M3</td>
<td>18</td>
</tr>
<tr>
<td>Mx</td>
<td>7</td>
</tr>
<tr>
<td>Degree of resection according to the surgery protocols and post-operative CT imaging or MRI:</td>
<td></td>
</tr>
<tr>
<td>total resection</td>
<td>29</td>
</tr>
<tr>
<td>subtotal resection</td>
<td>22</td>
</tr>
<tr>
<td>Disease progression*</td>
<td>17</td>
</tr>
<tr>
<td>Lethality*</td>
<td>11</td>
</tr>
<tr>
<td>for the age of:</td>
<td></td>
</tr>
<tr>
<td>0–12 months</td>
<td>1</td>
</tr>
<tr>
<td>13–24 months</td>
<td>1</td>
</tr>
<tr>
<td>25–36 months</td>
<td>9</td>
</tr>
<tr>
<td>for sex:</td>
<td></td>
</tr>
<tr>
<td>girls</td>
<td>5</td>
</tr>
<tr>
<td>boys</td>
<td>6</td>
</tr>
</tbody>
</table>

Note. * Follow-up data were known for 43 patients.

delberg, Heidelberg, Germany). The data on molecular subtype were known for 47 patients.
The data on the detected aberrations in chromosomes 2p, 8q, and 17q are listed in Table 2.

A Kaplan-Meier analysis of the survival rate in medulloblastoma patients younger than 3 years of age has demonstrated that desmoplastic/nodular medulloblastoma has a positive predictive value for progression-free survival only (Fig. 9), which was supported by the Cox regression model (Fig. 10).
Fig. 10. Effect of the histological type of medulloblastoma on progression-free survival rate in children younger than 3 years of age (Cox regression model).

Medulloblastomas belonging to the SHH molecular subtype were found to exhibit the most favorable indicators of overall and progression-free survival (Figs. 11, 12); the data on progression-free survival only were supported by the Cox regression model (Fig. 13).

Fig. 11. Effect of the molecular subtype of medulloblastoma on progression-free survival rate in children younger than 3 years of age.

Fig. 12. Effect of the molecular subtype of medulloblastoma on overall survival rate in children younger than 3 years of age.

Fig. 13. Effect of the molecular subtype of medulloblastoma on progression-free survival rate in children younger than 3 years of age (Cox regression model).

Fig. 14. Analysis of lethality in medulloblastoma patients younger than 3 years of age depending on a molecular subtype of medulloblastoma.
The effect of clinical factors (patient’s sex and age, tumor localization, degree of resection, and the M status) and genetic aberrations on survival indicators was unreliable.

An analysis of fatal outcomes depending on medulloblastoma belonging to a certain molecular subtype (Fig. 14) and clinico-morphological factors was carried out (the data are summarized in Table 3). The subtype C was found to have the most unfavorable indicators: the rate of lethality in this group was 50% (as opposed to 17% for subtype D). The subtype SHH was the most favorable group in terms of its prognostic value (13% lethality rate).

### Discussion

Our cohort of medulloblastomas in children younger than 3 years of age consisted of 51 tumors collected during a 10-year period at the Neurosurgical Institute, Russian Academy of Medical Sciences, which is one of the largest series of this type of tumors described in literature. The largest series of 96 medulloblastomas that has been described by D. Johnston et al. [10] is a group collected by 17 Canadian Medical Centers over the period from 1990 to 2005.

According to our data, desmoplastic/nodular medulloblastoma, which is characterized by aberrant regu-

### Table 2. The detected aberrations in chromosomes 2p, 8q, 9q, and 17 in medulloblastoma patients under 3 years of age

<table>
<thead>
<tr>
<th>Patient’s sex and age</th>
<th>Histological type of medulloblastoma</th>
<th>MYC amplification (n=2; 4%)</th>
<th>MYCN amplification (n=4; 8%)</th>
<th>Isochromosome 17q (n=8; 16%)</th>
<th>9q deletion (n=4; 8%)</th>
<th>Follow-up data</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, 2 years 6 months</td>
<td>Large cell/anaplastic</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Died of disease progression 18 months later</td>
</tr>
<tr>
<td>M, 3 years</td>
<td>Same</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Died of disease progression 6 months later</td>
</tr>
<tr>
<td>M, 1 year 7 months</td>
<td>Desmoplastic/nodular</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>Alive 51 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>F, 2 years 5 months</td>
<td>Same</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Alive 27 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 3 years</td>
<td>Large cell/anaplastic</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>Alive 11 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 2 years 11 months</td>
<td>Same</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Alive 10 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 3 years</td>
<td>Desmoplastic/nodular</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Alive 100 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 2 years 2 months</td>
<td>Same</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Died of disease progression 15 months later</td>
</tr>
<tr>
<td>F, 2 years 10 months</td>
<td>Same</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>Alive 46 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 1 year 6 months</td>
<td>Same</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Alive 60 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 11 months</td>
<td>Same</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Alive 48 months after surgery; no signs of disease progression</td>
</tr>
<tr>
<td>M, 1 year 10 months</td>
<td>Classical</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>Alive 3 months after surgery; no signs of disease progression</td>
</tr>
</tbody>
</table>

*Note. Here and in Table 3: M – male; F – female.*
Table 3. Analysis of the lethal cases in medulloblastoma patients under 3 years of age

<table>
<thead>
<tr>
<th>Patient’s sex and age</th>
<th>Localization</th>
<th>Degree of resection</th>
<th>M status at the moment of diagnosis</th>
<th>Histological type</th>
<th>Aberrations</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>M, 6 months</td>
<td>Vermis cerebelli</td>
<td>Total resection</td>
<td>Mx</td>
<td>Classical medulloblastoma</td>
<td>ND*</td>
<td>Disease progression</td>
</tr>
<tr>
<td>M, 2 years</td>
<td>Same</td>
<td>Subtotal resection</td>
<td>M0</td>
<td>Same</td>
<td>ND</td>
<td>Same</td>
</tr>
<tr>
<td>M, 2 years 2 months</td>
<td>Giant tumor in PCF</td>
<td>Total resection</td>
<td>M0</td>
<td>Desmoplastic/nodular</td>
<td>Isochromosome 17q</td>
<td>Same</td>
</tr>
<tr>
<td>M, 2 years 2 months</td>
<td>Vermis cerebelli and cerebellar hemisphere</td>
<td>Same</td>
<td>Mx</td>
<td>Same</td>
<td>ND</td>
<td>Same</td>
</tr>
<tr>
<td>F, 2 years 6 months</td>
<td>Vermis cerebelli</td>
<td>Subtotal resection</td>
<td>M1</td>
<td>Large cell/anaplastic</td>
<td>MYC oncogene amplification</td>
<td>Isochromosome 17q</td>
</tr>
<tr>
<td>M, 2 years 7 months</td>
<td>Same</td>
<td>Same</td>
<td>M3</td>
<td>with extensive nodularity</td>
<td>ND</td>
<td>Complications of chemotherapy</td>
</tr>
<tr>
<td>F, 3 years</td>
<td>Vermis cerebelli and cerebellar hemisphere</td>
<td>Total resection</td>
<td>M0</td>
<td>Classical</td>
<td>Same</td>
<td>Disease progression</td>
</tr>
<tr>
<td>F, 3 years</td>
<td>Vermis cerebelli</td>
<td>Same</td>
<td>M3</td>
<td>Same</td>
<td>Same</td>
<td>Complications of chemotherapy</td>
</tr>
<tr>
<td>F, 3 years</td>
<td>Same</td>
<td>Subtotal resection</td>
<td>M0</td>
<td>With extensive nodularity</td>
<td>Same</td>
<td>Disease progression</td>
</tr>
<tr>
<td>M, 3 years</td>
<td>Same</td>
<td>Total resection</td>
<td>M2</td>
<td>Classical</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>M, 3 years</td>
<td>Same</td>
<td>Same</td>
<td>M3</td>
<td>Large cell/anaplastic</td>
<td>MYC oncogene amplification</td>
<td>Isochromosome 17q</td>
</tr>
</tbody>
</table>

Note. PCF – posterior cranial fossa. *ND – not detected.

lation of the SHH signaling pathway and can develop from the precursor cells of the outer granular layer of the cerebellum [8] and from the cochlear nucleus of the brain stem [9], is the predominant histological variant of medulloblastoma in children under the age of 3. Some authors [8] have emphasized the direct association between the desmoplastic/nodular histological type and tumor localization in a cerebellar hemisphere; however, the tumors in our series typically localized in the median part of the cerebellum or, less frequently, affected the vermis cerebelli or a cerebellar hemisphere. Pure localization of medulloblastoma in a cerebellar hemisphere was observed only in 8% of cases, taking into account the fact that the desmoplastic/nodular histology occurred in 57% of patients.

We have also observed two unique cases of metastasis of the desmoplastic/nodular medulloblastoma during a similar period (approximately 1 year after the tumor had been removed) in boys of the same age (~ 2 years old); one of them died of disease progression 20 months after surgery.

According to the published data [21, 24], the frequency of aberrations (MYC or MYCN oncogene amplification, isochromosome 17q) detected in the group of medulloblastoma children younger than 3 years of age does not significantly differ from the detected aberrations in medulloblastoma children of older age. The combination of large cell/anaplastic medulloblastoma and the detected MYC oncogene amplification and isochromosome 17q was characterized by a strict correlation with the fatal outcome: both patients died of disease progression 6 and 18 months later, respectively.

The frequency of MYCN oncogene amplification was twice as high in 8% of cases and was also associated with isochromosome 17q; however, these tumors typically had desmoplastic/nodular histology and exhibited a relatively positive outcome. The prognostic value of MYCN oncogene amplification has not been determined thus far. A. Korshunov et al. [13] have demonstrated the biological heterogeneity of non-SHH medulloblastomas with MYCN oncogene amplification by isolating the positive (the combination of MYCN amplification and 10q deletion) and unfavorable (MYCN oncogene amplification with the balanced profile of chromosome 10q) subtypes.

9q deletion emerges only in desmoplastic/nodular medulloblastomas that are characterized by deletion of the PTCH1 gene (locus 9q). This aberration was detected in 8% of patients, although some researchers [21] have reported that it occurs at a frequency of over 50%.

No 6q deletion or nuclear expression of β-catenin have been detected among 51 cases of medulloblastoma, which is in agreement with the data obtained by M. Kool [11] and M. Taylor [31] for children of different age in the WNT group.
Summarizing the aforementioned facts, it is obvious that the desmoplastic/nodular histological type is the most particular variant of medulloblastoma in children younger than 3 years old gives grounds to expect a favorable outcome, on one hand [16, 28]: the 5-year progression-free survival rate in our series was 76%. The possibility of maturation yielding well-differentiated ganglion tumors has been described for medulloblastoma with extensive nodularity, the most favorable variant of desmoplastic/nodular tumor in terms of its prognostic value [6, 7]. On the other hand, it is desmoplastic/nodular medulloblastomas that emerge in patients with Li–Fraumeni syndrome [17, 18, 25]; chromothripsis dular medulloblastomas that can also emerge in patients with Gorlin syndrome [18, 30]; radiation therapy of these tumors is complicated by the development of secondary nevoid basal cell carcinoma at the previously irradiated spots [29].

Children under 3 years of age are believed to have the lowest survival rate indicators as compared to those in older children. The reason for that is either the more aggressive medulloblastoma biology in very young children or the fact that radiation therapy was not included in the treatment protocol [19, 20] because of the risk of neuroendocrine (growth hormone deficiency, gonadal lesion, hyper- and hypofunction of the thyroid gland, thyroid nodule formation, hyperprolactinemia, adrenocorticotropic hormone deficiency, osteopenia, osteoporosis, obesity, lipid metabolism disorders, and metabolic syndrome) and neurocognitive effects (a decrease in IQ; deteriorated acquisition of oral language, reading, writing and mathematics; disturbances of short- and long-term memory), as well as hearing and vision disorders, kyphosis, vertebral demineralization and secondary tumors, in particular in patients with Turcot and Gorlin syndromes [15, 20, 26].

According to S. Leary et al. [16] and S. Rutkowski [27], nonmetastatic desmoplastic/nodular medulloblastoma (at the moment of diagnosis) in children under 3 years of age can be sufficiently treated by intensive chemotherapy without using radiation therapy, methotrexate, or high-dose chemotherapy with stem cell support. Patients with anaplastic/large cell medulloblastoma and the initial metastatic disease need to receive high-dose chemotherapy and craniospinal radiation [20].

However, according to some authors [4, 10], young children who have received radiation therapy exhibit a higher survival rate as compared to those treated without it. In this context, the development of modern radiation therapy techniques seems to be rather promising [5].

**Conclusions**

This study has illustratively demonstrated that desmoplastic/nodular medulloblastoma predominates in children under 3 years of age and has a positive prognostic value for progression-free survival only. Radiation therapy for desmoplastic/nodular medulloblastoma in children under 3 years of age can be used only in the case of tumor recurrence.

Another biological feature of medulloblastoma in children younger than 3 years of age is that it is not characterized by nuclear accumulation of β-catenin and chromosome 6q deletion. Medulloblastomas with MYCN oncogene amplification are more likely to be characterized by desmoplastic/nodular histology and a relatively favorable outcome. Detection of MYC oncogene amplification is the most unfavorable prognostic factor; these tumors should be included in the high risk protocol.

**REFERENCES**


Clinical progression is not always obvious (some mutations are encode between the genetic mistakes, the histological presentation, and the periodical literature thus far. Although the association between the genetic mistakes, the histological presentation, and clinical progression is not always obvious (some mutations are detected in different histological subtypes, sometimes in the form of combined mutations, etc.), a clear relationship between the identified molecular subtype and prognosis can be traced in most cases. Thus, according to the data obtained by the authors, the SHH subtype has demonstrated the best results both for the overall and progression-free survival rate.

Furthermore, I would like to bring your attention to the really large group of medulloblastomas in children under 3 years of age. The fact that the desmoplastic/nodular medulloblastoma type is the predominant one according to the results of this study, while it has been reported in recent publications that the variant with extensive nodularity predominates in children at the age of 2—3 years, is of certain interest. I believe that this paper will be useful for experts (mainly for neuro-oncologists and neuropathologists), since it contains a rather concentrated pool of data on genetics and pathohistology of medulloblastoma in children under 3 years of age and their association with patient survival.

A.N. Kislyakov (Moscow)
The urgency of the meningioma challenge is associated with the wide occurrence of this type of tumors. According to the reports of the Central Brain Tumor Registry of the United States (CBTRUS), meningiomas account for 35.5% (followed by gliomas accounting for 31%) in the total incidence rate of primary central nervous system tumors (20.59 per 100,000 population per year). Correspondingly, the annual incidence rate of meningiomas is 7.2 per 100,000 population. This indicator increases with patient’s age, aggravating the problem with allowance for the fact that the proportion of older adults is increasing in the industrialized countries. Meningioma is the most frequent CNS tumor among patients older than 35. In patients aged 85 and older, the annual incidence rate of meningiomas is 7.2 per 100,000 population. This indicator increases with patient’s age, aggravating the problem with allowance for the fact that the proportion of older adults is increasing in the industrialized countries. Meningioma is the most frequent CNS tumor among patients older than 35. In patients aged 85 and older, the annual incidence rate of meningiomas reaches 46 cases per 100,000 population and is over threefold higher than the incidence rate of gliomas [13]. The prevalence of meningiomas is 97.5 per 100,000 population; there are 170,000 patients with verified meningiomas in the United States today [27].

Materials and Methods

A total of 15,143 patients with meningiomas of different localization were operated on at the Burdenko Neurosurgical Institute during the period 1932–2011; their number in 2011 alone was 664. A statistical analysis was performed using the Russian-language version of the Statistica 6.0 software. The descriptive statistics methods were mostly used to analyze the data; the Mann–Whitney nonparametric test, the Kruskal–Wallis test, the nonparametric correlation test (gamma correlation), the chi-square test, and Fischer’s exact test were used in selected patient groups. Differences were considered significant at p<0.05.

Results and Discussion

The meningioma challenge was studied at the Burdenko Neurosurgical Institute since the time it was established [1]. This field of research was initially supervised by K.G. Terian [7], who defended his PhD thesis in 1937 and published his monograph named “Cerebral Meningiomas” in 1941. The meningioma research program was adopted in 1937 at the 3rd Session of the Board of Neurosurgery; however, the preparations for World War II have brought about significant changes in research areas being intensely studied. The studies focused on neurooncology were not any longer conducted after the war started. The number of patients operated on decreased dramatically, while the postoperative mortality increased (Fig. 1). Thus, whereas 37 patients with meningiomas were operated on at the Burdenko Neurosurgical Institute (with the postoperative mortality of 35%), only 24 patients were operated on during the period 1942–1944 and 11 (45.8%) of them died.

The meningioma research was continued during in the postwar era. A gradual reduction in postoperative...
mortality was observed along with the increased number of patients. The level of postoperative mortality started to decrease reliably in 1975, which can be attributed to the improved diagnostic accuracy and beginning of using microsurgical equipment to manage tumors. This indicator has dropped to 2% over the next eight years and has been ~1% during the past decade. Most lethal outcomes are nowadays caused by the concomitant pathology.

The improvement in outcomes of managing patients with meningiomas was observed after the modern neuroimaging techniques (3D CT and MR angiography, perfusion tests, etc., which allow one to assess both the attitude of a tumor to the surrounding structures as well as the degree of its blood supply, surgical density, and probability of brain infiltration) started to be used in everyday practice.

It is noteworthy that the decrease in postoperative mortality took place simultaneously with the change in the structure of patients (Fig. 2). In 1932–1939, patients with tumors of parasagittal and convexital localization accounted for 72% of all the patients managed at the Burdenko Neurosurgical Institute. The share of this type of patients has reduced to 51% by 1985, while the share of patients with meningiomas of the skull base increased simultaneously. This ratio has recently changed to an even greater extent: the patients with parasagittal and convexital meningiomas account for 34%; most surgeries are performed for meningiomas of the skull base and disseminated tumors that spread to more than a single anatomical region. This trend can be attributed to the fact that it is patients with the most complicated pathology (including the ones with skull base meningiomas) that are admitted to the Institute. The patients with convexital tumors are mostly operated at the point of hospitalization.

It should be mentioned that while only 100 patients with meningiomas of the base of posterior cranial fossa were operated on during the period 1932–1959 (with 22% postoperative mortality rate), the same number of

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![Fig. 1. Number of patients and postoperative mortality rate for intracranial meningiomas (1932–2010).](image1)

![Fig. 2. Distribution of meningiomas with respect to their localization.](image2)
patients were operated in 2011 alone (with 0% mortality rate).

The functional outcomes of surgeries have also improved. The dynamics of the Karnofsky performance score [15] at discharge and 1 year after the surgery was followed up in groups of patients with parasagittal meningiomas (Fig. 3). It is clear from Fig. 3 that whereas in the early 1960s, an average patient discharged from the Neurosurgical Institute was disabled, today he/she can quickly return to his/her regular occupation.

The gender structure of patients with meningiomas operated on at the Neurosurgical Institute has also changed. A significant predominance of female patients among the patients with meningiomas has been reported since the Cushing’s study [12]. According to the Central Brain Tumor Registry of the United States, this ratio is currently equal to 2.2:1 [13]. However, our data showed an insignificant predominance of female patients during the Soviet period until the mid-1980s (the female : male ratio being 1.27:1) (Fig. 4). Nevertheless, the ratio has been corresponding to the “western standards” over the past decade (2.7:1). We cannot interpret the reason for this dependence. It might be of interest for sociological research.

Throughout the entire history of the Burdenko Neurosurgical Institute, much attention has been paid to studying the catamnesis of patients operated on. The correspondence and data of outpatient examination were stored; the patients filled out questionnaires, surveys, etc. When analyzing these data, we have ascertained that the frequency of recurrent meningioma during the period of at least 15 years after the primary surgery decreased from 40% (in the 1960s) to 29% (in 1996) (Fig. 5). The extrapolation of the detected regularity gives grounds to assume that the average risk of a recurrence or continued growth of intracranial meningiomas in the patients operated on is now ~25%. The data reported in the largest series of observations that have been published (none including more than 1,000 cases) are comparable. This index cannot be regarded as satisfactory. It is clear that meningioma recurrence is currently the main challenge in managing patients with these common tumors.

The radical primary surgery, histological malignancy of the tumor, and radiation therapy are the factors having an independent effect on probability of meningioma recurrence [14].

Our data (in terms of an example of a group of patients with parasagittal meningiomas) support the great significance of radical surgical interventions (Fig. 6). However, as can be seen in Fig. 6, the probability of recurrent parasagittal meningioma by the time 15 years after the surgery was as high as 25% even after the surgeries with the highest degree of radicality (Simpson grade I [22]) performed before 1995.

One of the reasons can be associated with the fact that assessment of the degree of radicality of excision of
meningioma is rather subjective. The research by K. Skullerud and A. Loken (1974), which has revealed the macroscopic remnants of the tumor during postmortem examination in 21% of cases when it had been radically removed, was the classical study of the pre-computer era [23]. The modern neuroimaging methods fail to detect a tumor smaller than 1 mm in diameter, including small remnants of tumor infiltration of the brain, cerebral meninges, vessels, and nerves. It is clear that the degrees of surgery radicality (Simpson grades I, II, and III) cannot be objectively verified even today [22].

The failure to comply with the principles of ablastics during a surgery in oncological patients is the major reason for high frequency of meningioma recurrence even after the tumors were seemingly completely resected. Since a tumor cannot be removed together with the surrounding tissues, while being resected via fragmentation instead, it is clear that several millions or (more frequently) billions of tumor cells remain in the wound even after the most radical intervention (let us remind that 1 mm³ of the tumor tissue contains 10⁸ cells). All neuro-oncological surgeries (even those that seem to be radical) are in fact cytoreductive by nature: it is either the major or minor portion of the tumor but never the entire tumor that is removed. The fate of the tumor cells remaining in the wound depends on their number, integrity of blood supply, molecular and biological parameters (which determine the “biological behavior” of meningioma), a number of insufficiently studied factors (including the immune response of the organism), and the use of additional therapy methods.

The prospects of improving the treatment outcomes in patients with meningioma are associated with continued research in efficient methods for reducing the number of tumor cells present in the patient’s organism. Two methods have been proved to be efficient thus far:

- surgical intervention;
- radiation therapy and radiation surgery.

Surgery. As it has already been mentioned, the maximum radical surgical resection was the first method to treat patients with meningiomas; it still remains the most efficient one. Similar to the other large clinics in the industrialized countries, the Burdenko Neurosurgical Institute has been designing and implementing the extensive surgical approaches to meningiomas of the skull base located in the hard-to-reach areas during the late XX century. The methods of plastic closure of the resulting defects were mastered and modified if necessary. The use of the Bichat’s fat ball as proposed by V.A. Cherekaev is the preferential approach [11]. A total of 34 reconstructive interventions on the superior sagittal sinus were performed. The degree of radicality of surgical interventions in patients with meningiomas of the base of the posterior cranial fossa has reached 81% [8].

However, it has been ascertained along with the accumulated experience that extensive neurosurgical approaches reliably worsen quality of life of the patients during the postoperative period [18]. We have revealed the fact of worsened quality of life in patients after the reconstruction or resection of the superior sagittal sinus blocked by a tumor behind the coronal suture. Since during the past several decades the surgical intervention is not any longer the only method to treat meningiomas, the modern neurosurgery is based on the principle that a surgery should cause no additional chronic invalidization of a patient.

Intraoperative photodynamic diagnosis, which is used to more accurately detect the location of a tumor lesion, is a potentially efficient method enabling one to enhance the radicality of meningioma removal. A group
of researchers under the supervision of RAS and RAMS academician A.A. Potapov are currently being focused on this area [6].

However, the facilities of significantly increasing the radicality of surgeries without deterioration of functional outcomes are rather limited during the current state of progress in neurosurgical equipment.

**Radiation therapy.** During a long time, meningiomas have been considered resistant to radiotherapy. Almost all researchers (including K.G. Terian [7], G.A. Gabibov [2], and D. Simpson [22]) held this viewpoint. Correspondingly, radiotherapy was seldom used, preventing one from arriving at any conclusions about its efficiency because of the insignificant number of observations. Thus, only 13 patients have received radiation therapy for meningiomas at the Neurosurgical Institute by 1985 [4]. For reference, radiation therapy has been performed in 12 patients with meningiomas (anaplastic only) at the Columbia University (United States) by 1984.

In 1980, J. Yamashita et al. [28] reported isolated cases of a significant increase in the inter-recurrence period when performing radiation therapy in patients with recurrent meningiomas. After that the radiation therapy started to be used more commonly. It became clear that the use of this type of therapy considerably improves the treatment outcomes for radically nonresected, biologically aggressive, and histologically malignant meningiomas.

The conventional radiation therapy is currently used in patients with all types of malignant meningiomas during the postoperative period [19], as well as with relapses of benign radically inoperable meningiomas [24]. The treatment outcomes are improved at least twofold in this case [9].

However, the conventional radiation therapy has reached its limits associated with the physical parameters of the beams of particles being used, since the low spatial gradient of the dose when high radiation doses are delivered to the focus inevitably increases the number of complications even if 3D computer-assisted planning was performed [5].

The way out of this situation is to implement precision stereotactically oriented radiation techniques into wide clinical practice, which ensure the doses lethal for cells over the entire tumor, while maintaining the minimal lesions of the adjacent tissues (i.e., 3D conformal radiation therapy and radiation surgery). The precision radiation has recently become a real alternative for surgical resection of meningiomas due to technological progress.

The radiation therapy is today believed to be associated with a lower risk of complications as compared to

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**Fig. 7.** Outcomes of irradiation of a female patient with benign meningioma on a Gamma Knife system

[SRS is used for stereotactic radiosurgery].
surgical interventions and to allow one to attain a high degree of tumor growth control that is comparable to that after radical surgery [21]. Radiation of benign meningiomas using modern techniques (radiosurgery and stereotactic conformal radiotherapy) allows one to attain high degrees of tumor growth control (over 90% during 10 years), while the number of complications is low (0–8%) [16, 19].

A total of 2280 patients with meningiomas have received radiation therapy at the Department of Radiology of the Neurosurgical Institute by the end of 2011.

Radiosurgery was used for solitary or multiple meningiomas of small size (up to 3–3.5 cm in diameter). Radiosurgical radiation of benign meningiomas typically employed the marginal doses of ~14 Gy (Gamma knife) (Fig. 7) or medium doses of 15–17 Gy (CyberKnife, Novalis).

The radiation in conventional fractionation regimen was used in patients with large meningiomas, as well as when the anterior optic tract was affected by the tumor and brain stem compression was rather severe. With allowance for the clear tumor borders and the necessity to protect the “critical” structures, stereotactic conformal radiation therapy in patients with benign meningiomas was performed using a Novalis system at single boost dose (SBD) of 1.8–2 Gy until the total boost dose (TBD) of 50–54 Gy was achieved.

In a significant number of cases, radiation therapy made it possible to stabilize the tumor size and symptoms. The tumor growth control was 96.8% for the mean follow-up period of 31.6 months. Partial tumor response (an average decrease in tumor volume by 3.25 cm³ (0.2–21.6 cm³) or by 16% (0.3–45.3%) was observed in 53% patients. Complete or partial regression of symptoms after the radiation was observed in 43% of cases; the initially disturbed visual function improved in 35% of patients. The aggravation of symptoms was observed in 8.7% of cases (usually when higher doses were em-

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**Fig. 8.** Example of significant decrease in meningioma size in response to radiation therapy
a, c – MRI before irradiation (Nov. 2009), the tumor is outlined in red; b, d – MRI recorded on Jan. 2011, the tumor is outlined in green.
ployed). The use of a SBD of 1.8 Gy until the TBD of 54 Gy in the isocenter is associated with the lowest risk of complications.

Figure 8 shows the outcome of radiation therapy in a female patient with meningioma of the median segments of the mesocranial fossa (on the left-hand side) on a Novalis linear accelerator. The tumor volume decreased from 13.5 to 9 cm$^3$ (by 33.3%) during 1 year. The visual field of the left eye was normalized.

Figure 9 shows another example of the effect of stereotactic conformal radiation therapy performed on a Novalis linear accelerator. A decrease in tumor remnants and the restoration of visual function is observed 2 years after the radiation of a partially resected meningioma of the skull base that was difficult to reach.

Figure 10 shows the outcome of radiation therapy in a patient with optic nerve meningioma with the preserved visual function. The radiation in these patients allows one not only to stop tumor growth but also to stabilize or improve the visual function. An example of this treatment is shown in Fig. 10.

Stereotactic radiation therapy is the only possible method for treating patients with optic nerve meningiomas with the preserved visual function. The radiation in these patients allows one not only to stop tumor growth but also to stabilize or improve the visual function. An example of this treatment is shown in Fig. 10.

The malignant anaplastic meningiomas require a more aggressive approach to be used. These tumors are typically irradiated in the conventional fractionation regimen up to SBD of 56–60 Gy, with the marginal capture of the tissues surrounding the tumor of ~1 cm.

Hypofractionation (i.e., the use of 3 (6–8 Gy each) to 7 fractions (4.5–5 Gy each) is the least unambiguous but the most promising procedure of meningioma irradiation [3]. This method combines the advantages of radiosurgery with smaller load on the critical structures. Irradiation using this procedure is performed at the Neurrosurgical Institute predominantly on the CyberKnife system. The use of hypofractionated radiation is particularly indicated for patients with a large tumor volume (over 14 cm$^3$), when radiation surgery is hazardous. The multiple beam and inverted planning options available for the CyberKnife system allow one to irradiate complex-shaped meningiomas and multiple meningiomas (up to 12 in the case shown in Fig. 11) in the hypofractionation regimen.

Radiation methods have for a long time been regarded as auxiliary procedures that supplement the results of surgical intervention. The term “adjuvant radiation therapy” was even made up. However, the roles of a surgeon and a radiologist have changed today. In patients with disseminated difficult-to-reach meningiomas, a radiologist and a medical physicist often assign a surgeon the task to reduce the tumor volume and/or provide a space between the tumor and the “critical” structures, such as the optic nerves, the chiasmus, and the brain stem. Such a complex multidisciplinary approach ensures the optimal treatment outcomes for the patients that were previously regarded as incurable.

Histological malignancy of the tumor is an independent factor affecting the outcomes of treating meningiomas [14]. This factor is independent not only in terms of statistics (i.e., according to the results of multivariate analysis not related to radicality of the surgery and performing radiation therapy) but also even does not depend on the facilities available. All neurosurgeons have encountered such situations when a meningioma rapidly progressed and caused death of a patient despite the combination therapy.
The methods for treating patients in such complex cases are currently being developed. No clinical recommendations for chemotherapy using cytostatic drugs, angiogenesis and immune therapy inhibitors (interferon drugs) in patients with meningiomas exist today. Intense research in this area is being performed at the Neurosurgical Institute, as well as in the other large clinics abroad. The possibility of using cyclooxygenase 2 in-
hibitors (Celecoxib), calcium antagonists (Verapamil), progesterone and retinoic acid antagonists, etc. are also taken into consideration.

Dexamethasone is a rather efficient auxiliary drug. Its mechanism of action is primarily related to a significant (3.2-fold as compared to the isoline) decrease in expression of the vascular endothelial growth factor by tumor cells [26] and other angiogenins. When penetrating to the cerebral tissue through the region where the tumor contacts the pia, these very proteins stimulate angiogenesis ensuring metabolism of the progressing tumor and are the main factor causing peritumorous brain edema. In fact, brain edema is a sanogenetic mechanism bolstering the reduction in angiogenin concentration in the intercellular space via dilution, which impedes pathological angiogenesis in the brain tissue. The anti-edematous effect of glucocorticosteroids is related to the suppressed secretion of angiogenins (and presumably metalloproteinases) by tumor cells; correspondingly, these drugs are useless in case of traumatic and ischemic brain edema.

Regardless of the fact that meningioma is the best-studied (in molecular biological terms) human solid tumor [29] and was supposed to be used to formulate the general theory of oncogenesis, the research into meningioma genetics and clinical use of the revealed regularities is far from being completed. The studied focused on the molecular biology of meningiomas are conducted at the Neurosurgical Institute in collaboration with A.G. Korshunov (currently working in Heidelberg, Germany).

Determination of the Ki-67 labeling index to evaluate the proliferative activity of cells is now a routine procedure performed in the Neurosurgical Institute (Fig. 12). Ki-67 labeling index higher than 4% was shown to unambiguously attest to biological malignancy of meningioma.

The prognostic significance of chromosome 9 deletion was ascertained by studying resected meningioma specimens via fluorescent in situ hybridization (FISH). It was revealed in 31 and 9% of cases of recurrent and nonrecurrent meningiomas, respectively. Deletion of the 9p21 locus was revealed only in the group of malignant meningiomas (Fig. 13). The study by A.G. Korshunov, V.A. Cherekaev, and A.Kh. Bekyashev devoted to the description of chromosomal aberrations associated with meningioma progression was recognized as the best study at the 13th European Congress of Neurosurgery in Glasgow [17].

The actual prospects can be associated with screening and, correspondingly, early diagnosis of meningiomas. The possibility of tumor diagnosis by detecting antibodies to antigens associated with tumor transformation of the cell has been intensively studied since the early XXI century [25]. In 2011, N. Ludwig et al. [20] demonstrated the feasibility of meningioma diagnosis using autoantibodies in blood serum for the first time.

![Fig. 12](image_url)

**Fig. 12.** Histological specimens (x400) of meningiomas of the skull base with the Ki-67 labeling index lower than 4% (a) and higher than 4% (b).
(with 95.6% specificity, 91.8% sensitivity, and 93.8% accuracy). The accuracy of this method can be increased by broadening the range of recombinant proteins used for the test.

Although the screening techniques have not been implemented into practice yet, the detection frequency of small meningiomas that clinically do not manifest themselves has recently significantly increased due to the wide use of CT and MRI. The expectant management is the optimal strategy for the incidentally detected meningiomas that cause no peritumorous brain edema. These patients need to undergo another contrast-enhanced MRI 3 months later and subsequently once every six months. Either surgical or radiation therapy is indicated in the following cases: increasing tumor size, emergence of peritumorous brain edema. These patients need to undergo another contrast-enhanced MRI 3 months later and subsequently once every six months. Either surgical or radiation therapy is indicated in the following cases: increasing tumor size, emergence of peritumorous brain edema and clinical manifestations. Decisions should be made individually for each particular situation, especially if the incidentally detected meningioma is larger than 2 cm and localizes near the functionally important structures; however, the fact of incidental diagnosis of intracranial meningioma in most cases is not an indication for therapy.

If early diagnosis of meningiomas is successfully implemented into clinical practice, it can be expected that the number of patients requiring neurosurgical interventions will be reduced significantly. In case of verified progression of a small meningioma, radiosurgery or stereotactically oriented radiation therapy will most probably be selected. However, taking into account the fact that the time between tumor emergence and manifestation of clinical symptoms is rather long (~20–30 years according to the data obtained by J. Wiemels et al. [27]), one should not expect that the number of patients operated on will decrease significantly within the near decades even if the screening procedure is implemented into practice.

**Conclusions**

1. Meningiomas are the most frequent primary CNS tumors; their annual prevalence is 7.2 per 100,000 population and significantly increases with age.
2. Contrast-enhanced MRI supplemented with other methods if necessary is the standard procedure for objective diagnosis of meningiomas.
3. Surgical intervention is an efficient but not the only therapy method for patients with meningiomas. The unjustified increase in radicality and the use of extensive surgical approaches worsen the functional outcomes.
4. The optimal outcomes in patients with radically incurable meningiomas are achieved by including the radiation methods (radiosurgery and 3D conformal radiation therapy) to the therapy complex.
5. Dynamic observation is the common strategy for the incidentally detected meningiomas. The surgical or radiation treatment is indicated if clinical symptoms, peritumorous brain edema, and/or tumor progression are observed.

**REFERENCES**

Lung Cancer Metastases to the Brain: Clinical and Morphological Prognostic Factors

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Brain metastases (BM) are the most frequent and extremely heterogeneous group of intracranial tumors from the morphological point of view. Nevertheless, until recently, little attention has been paid to histogenesis of the primary tumor in studies devoted to BM. Lung carcinoma is the most common source of BM; morphologically, this is a very heterogeneous group of tumors, and they demonstrate different clinical pathways and outcomes. The aim of the present study was to evaluate the clinical and morphological prognostic factors in 126 patients with lung carcinoma metastases to the brain, who were operated on in 2004—2010 at the Burdenko Neurosurgical Institute. Statistical analysis demonstrated that the age, gender, amount and location of BM, primary operation, and even histological tumor type were not significant prognostic factors, while the absence of extracranial metastases and Karnofsky index above 70 were significant factors of favorable prognosis.

Keywords: lung carcinoma, brain metastases, prognostic factors.

The frequency of brain metastases (BM) is 5—10 times higher than that of malignant gliomas [8]. The problem of BM remains insufficiently studied despite the fact that it is rather urgent in a number of medical disciplines, such as neurosurgery, oncology, pathological anatomy, etc. The questions related to diagnosis, treatment, and prognostic factors of BM have conventionally been discussed independently of histogenesis and localization of the primary tumor [9, 11]. Few studies have recently been published [2, 5], in which BM are investigated in their inseparable association with histogenesis and localization of the primary tumor.

Lung carcinoma (LC) is the most frequent tumor metastasizing to the brain [8, 12]. The prevalence of BM in patients with LC is attributed to blood supply, the anatomical proximity of lungs to the brain, and other features of LC metastases to the central nervous system (CNS) [8, 12]. In turn, the high incidence rate of LC in Western Europe and North America, as well as in Russia, is the reason for the high frequency of lung cancer metastases to the brain.

LC is known to be a heterogeneous group of tumors that differ in terms of histogenesis, biological behavior, immunohistochemical markers, and prognosis, which requires differentiated approaches to be applied when treating patients [6]. The large number of clinical studies focused on the efficiency indicators of various treatment protocols is determined by the high social importance of LC [1, 3]. Despite the fact that the phenotypes of the primary tumor and metastases (including BM) with respect to the major immunohistochemical markers are virtually identical [4, 5, 10, 13], the studies devoted to biological behavior of LC BM remain poorly systematized and no prognostic factors have been reliably ascertained.

This work was aimed at studying the prognostic value of clinical and morphological indicators in patients with LC metastases to the brain.

Materials and Methods

During the period of 7 years (January 1, 2004 — December 31, 2010), 786 patients with BM received neurosurgical or combined treatment at N.N. Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences. Among them, 126 patients were diagnosed with LC as the primary tumor. The patients with spinal metastases and BM without the revealed primary tumor by the time they had been discharged from hospital were excluded from the study.

The following clinical indicators were analyzed: patient’s gender and age, smoking history, the Karnofsky index (KI) at hospital admission, primary localization of the tumor and its histological type, localization and amount of BM, the presence of extracranial metastases, the number of neurosurgical operations, and previous treatment for the underlying disease and BM.

The long-term treatment outcomes were elucidated using patient-completed questionnaires. In order to refine the histological type of BM after neurosurgical interventions, the archived specimens stained with hematoxylin and eosin according to the conventional protocol were independently examined by two autopsists. If the conclusion could not be interpreted unambiguously, an immunohistochemical assay using an antibody panel (cytokeratins 5/6 and 18, thyroid transcription factor 1

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(TTF-1) and synaptophysin (DAKO), napsin A and p63 (Cell Marque)) was carried out to ensure the differential diagnosis and elucidate the tumor phenotype (see Table). The En Vision Flex visualization system (DAKO) was used. The Kaplan–Meier method was employed to analyze the survival rate. The reliability of differences between the survival curves was verified by the log-rank test using Statistica 8.0 software for Microsoft Windows. The confidence interval was assumed to be \( p<0.05 \).

**Results**

Among 126 patients who had been operated on for verified LC BM, males were predominating (98 males, 28 females); mean age was 56 years (28–79 years). 106 patients (84.1%) underwent a single surgical intervention; 18 (14.3%) and 2 (1.6%) patients underwent two and three surgeries, respectively. The overall condition of patients at hospital admission was assessed using the KI. The index varied from 30 to 100, scoring 70 and higher in 67.5% of cases.

The primary tumor localized in the left lung in 45 (35.7%) patients and in the right lung in 71 (56.3%) patients. Bilateral lesion was observed in 4 cases. No data on the side of the primary tumor have been obtained for 6 patients. The results of examination of the affected lobe were available in 61 cases only. The superior lobe was affected slightly more frequently (35 patients). LC localized in the inferior lobe in 23 patients. In one case, LC affected only the middle lobe of the right lung; bilateral lesion was observed in two cases.

Surgical intervention for the primary tumor was carried out in 53 (42.1%) patients. The data on previously conducted chemotherapy and/or radiation therapy for primary tumor were reported for 50 patients.

The clinically significant extracranial metastases were verified in 44 (35%) patients. In 79 (63%) patients, BM localized only above the tentorium of cerebellum. Solitary brain metastases were observed in 76 (60.3%) patients. Two BM occurred in 19 (15.1%) patients. Multiple BM (3 and more) were diagnosed in 31 (24.6%) patients.

Radiation therapy during the postoperative period was performed in 46 (36.5%) patients. The recurrent BM with subsequent neurosurgical treatment were observed in 40 (31.7%) patients.

The verified histological types of tumors were as follows: adenocarcinoma (ADC) with frequency of 58.7% (74 patients) (Fig. 1), small cell carcinoma (SCC) – 23.8% (30), and squamous-cell carcinoma (SqCC) – 17.5% (22) (Fig. 2).

The predominance of male patients was observed among the patients with BM of all histological types. The male : female ratio was 10:1, 6:1, and 2:1 for SqCC, SCC, and ADC, respectively.

All the patients with SqCC, 20 patients with SCC, and 37 patients with ADC were smokers. Direct association between gender, age, and smoking habits was

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**Fig. 1.** Immunohistochemical expression of TTF-1 in nuclei of metastatic cells of lung ADC in the brain. x200.

**Fig. 2.** Immunohistochemical expression of cytokeratin 5/6 in the cytoplasm of metastatic cells of SqCC in the brain. x200.
determined in patients with LC BM: men and older individuals were more likely to smoke.

A stable reverse correlation between patients’ age (younger or older than 50 years) and KI (below or above 70) was revealed ($r = -0.25$ at $p < 0.05$). $KI > 70$ correlated with the presence of another non-surgical treatment for the underlying disease in patient’s medical history. $KI > 70$ also correlated with the histological type of small cell or non-small cell LC.

In order to statistically process the data, the patients were subdivided into two groups using two methods:

1) patients with $KI \leq 70$ (89 patients, 70.6%) and $KI > 70$ (37 patients, 29.4%);
2) patients with $KI < 70$ (41 patients, 32.5%) and $KI \geq 70$ (85 patients, 67.5%).

Primary lesion of the right lung was predominant in both groups of patients with non-small cell CL; while the ratio was almost equal in patients with SCC (left and right lungs in 13 and 12 cases, respectively). Bilateral lung lesion was observed in 2 patients with SCC brain metastases and 3 patients with ADC brain metastases.

According to the current oncological standard treatment protocols, 24 patients with SCC brain metastases were not subjected to surgery for the primary tumor. In the group of patients with SqCC, the preliminary lung surgeries were performed in most patients with BM (12 (54.5%) patients). In the ADC group, 37 (50.0%) patients were operated on. Two patients (with SqCC and ADC) underwent lung surgeries after the neurosurgical intervention.

The presence of clinically significant extracranial metastases during the neurosurgical surgery was observed in 10 (33.3%) patients with SCC, 9 (40.9%) patients with SqCC, and 24 (32.4%) patients with ADC.

The isolated supratentorial lesion was frequently observed at all histological types; the ratios being approximately equal: ADC – 70.0% (51 patients); SqCC – 77.2% (17); and SCC – 63.3% (19).

The isolated infratentorial lesion was observed rather rarely: in 7 (9%) patients in the ADC group and in 5 patients (21%) in the SqCC group. The combined lesion most frequently occurred in the SCC group patients (9 cases, 30%), which is in agreement with the number of BM: multiple BM (3 and more) were diagnosed in 13 (43.3%) SCC patients. On the contrary, isolated lesions were predominant in patients with non-small cell types of cancer: SqCC – 68.2% (15 patients), ADC – 60.8% (45). Solitary BM in patients with SCC occurred in 14 (46.7%) cases.

The largest number of neurosurgical surgeries was performed in patients with ADC brain metastases: 61 (57.5%) patient among the individuals who underwent a single surgery; 10 (55.6%) patients among the individuals who underwent two surgeries; and 2 patients who underwent three neurosurgical operations.

The cumulative survival rate was reliably higher in the group of patients who had no extracranial metastases, as compared to the group of patients who were diagnosed with these lesions ($p=0.00391$) (Fig. 3). The overall survival in the group of patients who underwent repeated neurosurgical operations for BM was also reliably higher as compared to the patients who underwent a single surgery ($p=0.03123$) (Fig. 4).

The survival rate among patients with LC BM at $KI > 70$ was reliably higher than that at $KI \leq 70$ ($p=0.008$) (Fig. 5). It is noteworthy that no reliable differences in the survival rates have been revealed in the group of patients with $KI > 70$ and $KI < 70$ ($p=0.42285$).

Gender, age, smoking in the medical history, the number of neurosurgical interventions, features of localization of the primary LC, and localization of BM had no effect on the overall survival rate in patients with LC BM. The histological type of a tumor had no effect.
on the prognosis as well. All three types were compared to each other (Fig. 6); ADC was compared to the remaining types; and SCC was compared to the other non-small cell types. According to the published data, ADC and SCC is the most favorable and unfavorable prognostic types, respectively \((p=0.27537\) and \(p=0.31651\)). An insignificant trend toward increasing survival rate in patients with the resected primary tumor was revealed; however, the differences were not statistically reliable \((p=0.27537\)). Non-surgical treatment in patient’s medical history had no effect on the prognosis.

### Discussion

Lung cancer is the most frequent source of intracranial lesions (16% of all BM), which shows its leading positions in this pathology. The feature of our series of patients with LC BM was the predominance of male smokers, as opposed to the studies carried out for other countries. Among the patients with SqCC, smokers constituted 100% of the patients with BM.

Surgical intervention (“cytoreduction surgery”), as well as chemotherapy and/or radiation therapy for the underlying disease, had no effects on the prognosis. Localization of the BM (supra- or infratentorial) had no effect on the survival rate. The presence of extracranial metastases is a reliable factor of the most unfavorable prognosis \((p=0.00391\)). The longer-term survival rate was observed in patients who underwent repeated surgeries \((p=0.03123\), which is indicative of the fact that the neurological treatment method plays a significant role in patients with LC BM.

A clear reverse correlation between the age group “younger and older than 50” and KI > 70 \((r = -0.25, p<0.05\) was observed. KI also correlated with the presence of non-surgical treatment for the underlying disease and with the histological type of BM in medical history.

The RPA classes are known to be a reliable prognostic indicator in patients with brain tumors. This indicator is composed of the KI, patient’s age, and control of the underlying disease (in our case, the presence or absence of extracranial metastases).

KI > 70 was a more favorable prognostic factor. The survival rate is higher at KI > 70 \((p=0.008\). These data, along with good survival rate in the absence of extracranial metastases, are in good agreement with the conception of the RPA classes and their important prognostic value in patients with BM. The survival rate is reliably higher in the group of patients who had no extracranial metastases \((p=0.00391\). Nevertheless, the patients’ age as an independent indicator had no prognostic value.

The predominance of ADC among the histological types of LC seems to be associated with selection of patients for neurosurgical management of BM. SCC is a rapidly progressing tumor characterized by frequent and rapid development of metastases, which often makes the neurosurgical intervention unpromising (condition severity, multiple BM). On the contrary, ADC is the most favorable type of LC from the prognostic point of view. It is in patients with ADC that the greatest advance in treating the metastatic forms of LC has attained: the patients survive more frequently until the development of BM.

The revealed absence of the prognostic value of histological types of BM needs to be further studied at the molecular level.

The trend toward higher survival rate in patients with the resected primary tumor and the absence of effects
of chemo- and radiation therapy on disease prognosis additionally supports the heterogeneity of BM and the demand for more personalized care of patients.

Conclusions

1. LC BM is a heterogeneous group of metastatic tumors in the brain with unique prognostic factors.

2. The presence of extracranial metastases and KI > 70 are the statistically reliable independent prognostic factors for LC BM.

3. It is reasonable to study the molecular biology markers within each histological type of LC BM.

4. Neurosurgical intervention is an important stage in treating patients with LC BM that allows one to improve the disease prognosis.

REFERENCES


Commentary

This work is devoted to studying the clinical and morphological indicators and their prognostic value in patients with lung cancer metastases to brain. There are very few studies focused on the prognostic factors of secondary (metastatic) CNS tumors in Russian literature. Nevertheless, this problem becomes more and more urgent with the development of targeted “personalized” therapy and the advance in treating malignant tumors of almost any localization. While the diagnosis of brain metastases used to be a death sentence for a patient, modern neurosurgery and oncology have the resources to enhance the survival and the quality of life. Hence, the original studies of the prognostic factors in patients with brain metastases are very important. The authors of this study have examined a number of indicators in order to reveal the factors significant for disease prognosis.

Lung cancer is a source of brain metastases more frequently than all other malignant tumors. Moreover, the high frequency of lung cancer makes the problem of studying its biological behavior to be both of medical and social significance.

Lung cancer is actually a group of tumors that are united only by the primary localization of the oncological process. The authors have ascertained that the presence of extracranial metastases is an unfavorable prognostic factor. This fact is important, since it indirectly attests to the advance of neurosurgery in treatment of metastatic disease.

According to the results of this study, the Karnofsky index > 70 is a favorable prognostic factor. No association between the prognosis and the histological type of metastatic tumor has been revealed and further research using the modern methods, including those at the molecular level, is required. The latter facts are in agreement with the modern concept of “personalized medicine”.

E.A. Moroz (Moskow)
Primary and Metastatic Ewing’s Sarcoma of the Skull Base — Case Reports and Comparative Analysis


N.N. Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences, Moscow, Russia

The aim of the present study was to evaluate and compare diagnostic and treatment modalities of primary and metastatic Ewing sarcoma (ES) of the skull base. Material and methods. We analyzed nine cases of the skull base ES patients operated in Burdenko Neurosurgical Institute from 2003 to 2011. Among them there were five cases of primary ES, the other four were of metastatic origin. Clinical history, neuroimaging and pathology data together with IHC are presented. Treatment options and results are discussed. Seven patients were operated transcranially, in the other two cases endoscopic endonasal operations were performed. Mean follow up was 11—92 months. Results. We did not reveal any pathological or IHC differences between primary and metastatic tumors. The labeling index Ki-67 was insignificantly higher in the metastatic tumors group. In one case the patient developed relapse of the metastatic tumour in the temporal bone; he underwent second surgery and died 7 months after the operation. Conclusion. Despite both metastatic and primary ES of the skull base are of malignant behavior, the long-term relatively good prognosis can be achieved when combined treatment, including surgery, chemotherapy and radiation is applied.

Keywords: Ewing’s sarcoma, metastasis, skull base, immunohistochemistry.

Ewing’s sarcoma (ES) is the second most common malignant bone tumor. It affects long bones in 47% of cases, flat pelvic bones — 29%, ribs and vertebrae — 12%, the mandibular bone and skull — 9% of cases [1, 12].

ES was first described by an American oncologist J. Ewing in 1921 as a “diffuse hemangioendothelioma of bone”. Since that time, a number of researchers have attempted at elucidating the real histogenesis of this tumor. Morphological, immunohistochemistry, and electron microscopy data show that this neoplasm is a “primitive mesenchymal tumor with multipotent differentiation” [17]. This phenomenon has been verified by studies based on cell lines and tissue sections [14–16]. A tumor with a similar histological presentation, immunohistochemistry and molecular genetic parameters was also described for soft tissues [20]. In combination with other current studies [specific translocations t(11;22) and t(21;22)], this gave grounds for using the term “Ewing sarcoma family of tumors” in literature more frequently [1, 3].

The highest incidence rate of bone ES is observed among 5–13-year-old patients. In 75% of cases, these tumors affect people younger than 20 years of age. ES constitutes 6—9% of all malignant bone tumors among children. There is a certain predominance of male patients; the male : female ratio is 1.6:1 [4, 12].

ES is characterized by an appreciably aggressive course. It has multicentric manifestation in 30% of cases, while there are distant metastases as early as a primary focus is detected in 14—45% of cases [5, 12].

Histopathologic parameters of ES include monotonous layers of cytoplasm-depleted monomorphic rounded cells, round nuclei, and small nucleoloi. The presence of PAS (periodic acid-Shiff staining)-positive grains in the cytoplasm of tumor cells is a typical pathomorphological feature; it indicates the glycogen is present and makes ES differ from other similar tumors, such as lymphoma and rhabdomyosarcoma. Molecular genetic analysis detects pathognomonic chromosomal translocations t(11;22)(q24;q12). Immunochemical expression of CD99 and transmembrane protein encoded by the MIC-2 gene are the additional data that verify the diagnosis [9–12]. Both primary and metastatic ES can affect the skull base.

A comparative analysis of the primary and metastatic ES of the skull base in patients operated on in the same hospital was carried out.

Materials and Methods

9 patients with ES of the skull base were operated on in the Burdenko Neurosurgical Institute over the period between 2003 and 2011. The tumor was primary in 5 cases, while being of metastatic origin in 4 cases.

As compared to the metastatic ES of the skull base, primary ES affects younger patients. In 3 patients, primary ES of the skull base was identified at the age below 3 years; the age of two other patients when diagnosed with primary ES was 16 and 58 years (Table 1).
Patients with skull-base metastases aged 13–20. The primary tumors developed in them at the age from 11 to 14 years. The period between the time when a primary tumor was detected and skull-base metastasis manifested itself varied from 24 months to 8 years.

Male patients predominated in our group. The male:female ratio was 5:4 (1.25:1).

Medical history plays the key role in differential diagnosis of the primary and metastatic ES. In all the cases of metastatic lesion of the skull base, the past medical history comprised the data on the primary tumor and previous therapy for the primary focus.

Localization of the tumor of the skull base was determined according to the CT and MRI data. Both CT and MRI were performed in 3 patients. Osteolytic changes in the form of destruction of bone structures yielding defects with irregular contours and small bone inclusions in tumors were seen in the CT scans in all patients (Fig. 1). However, the CT data are insufficient to perform a thorough diagnostics and determine the therapy strategy. Hence, all patients with ES of the skull base underwent an MRI of the brain with intravenous contrast.

According to the MRI data, the tumors mostly had heterogeneous polynodular structure, contained cysts, necrotic and hemorrhagic foci. The tumor tissue is hyperintense compared to normal brain and hypointense compared to liquor on T1 MRI. In case of MRI with intravenous contrast, tumor intensely and inhomogeneously accumulates the contrast agent (Fig. 2).

The CT and MRI data in patients with primary ES are virtually identical to those in patients with metastatic tumors. In the latter case, necrotic foci and cystic transformations are frequently detected.

Among the skull base structures, the petrous temporal and cuneiform bones were most commonly affected both in patients with primary ES and in those with metastases (Table 2).

In this group of patients with 4 cases of metastases, the tumor affected the basilar and bones in 2 and 2 cases, respectively.

### Table 1. Age distribution of patients

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—5</td>
<td>3</td>
</tr>
<tr>
<td>6—10</td>
<td>0</td>
</tr>
<tr>
<td>11—15</td>
<td>2</td>
</tr>
<tr>
<td>16—20</td>
<td>3</td>
</tr>
<tr>
<td>Older than 20</td>
<td>1</td>
</tr>
</tbody>
</table>

Among the primary tumors, the tumor originated from the petrous temporal bone in two cases and from the occipital bone (while propagating to the areas of the occipital condyle and the jugular foramen) in one case. The basilar bone was affected in one case. In one patient, the tumor affected the frontal, temporal, and cuneiform bones.

The clinical presentation is caused by localization and the area to which the tumor has spread, while being independent of the fact whether it is primary or secondary. While the cases of calvarial lesions accompanied by headache and increased intracranial pressure have been predominantly reported in literature, the lesion of the skull base is primarily associated with the symptoms of cranial nerve lesions.

The general brain lesion symptoms (headache, nausea, and vomiting) were observed in 2 cases (Table 3). The general brain lesion symptoms in the form of sleepiness, adynamicity, and upward gaze paresis were observed in a 3-year-old child with a widespread tumor of the skull base and extensive effect on the brain, which resulted in edema and dislocation with compression of the 4th ventricle.
Lesion of the basilar bone mostly resulted in ocular motility and facial sensitivity disorders. When the tumor localized within the petrous temporal bone, the clinical presentation mostly consisted of the symptoms of lesions of the facial and auditory nerves.

In one case, the lesion of the occipital bone and spreading of the tumor to the jugular foramen, occipital condyle, and the petrous temporal bone resulted in lesion of nerves IV, V, VII, IX, X, XII.

Results

Combined therapy including surgical evacuation of the tumor followed by chemo- and radiation therapy was used in all 9 cases. When performing surgical interventions, the surgeons sought to attain the maximum degree of tumor resection. While a neoplasm in patients with calvarial tumors can easily be totally removed, this procedure is almost infeasible in patients with tumors of the skull base because of the involvement of the functionally significant structures. The tumor was removed transcranially in 7 cases; subtotally and totally, in 3 and 4 cases.

The endoscopic transnasal approach to the tumors of the basilar bone was performed in two patients. In one of the patients, the surgical intervention was confined to biopsy and removal of the available tumor portion from the sphenoidal sinus. The main portion of the tumor localized in the medial regions of the mesocranial fossa, in the cavernous sinus. For this reason, a decision was made to abstain from removing it. Endoscopic subtotal removal of the tumor was performed in the other case.

RCT I and RCT II chemotherapy was performed in 3 and 5 patients, respectively. The number of courses varied from 8 to 10. In one case, the long-term outcome of a patient after he had been discharged from the hospital was not followed. In the remaining 8 cases, chemotherapy was followed by radiation therapy with the TBD varied from 30 to 50 Gy.

After the surgical intervention, 8 out of 9 patients were followed up during the period from 11 to 92 months. In patients with metastatic tumors, the catamnestic observations were carried out for 11–34 months; in patients with primary tumors, for 18–92 months. We failed to follow up a 58-year-old patient with primary tumor of the petrous temporal bone after his discharge from the hospital. A relapse of metastatic tumor to the petrous temporal bone was observed in one patient 7 months after the metastasis was removed. The patient died 7 months after the reoperation because of generalization of the oncological process. Two patients with metastases to the basilar bone died of extracranial metastases three years after the metastasis had been removed. The patient with metastasis to the petrous temporal bone is followed up for 14 months without any signs of recurrence and extracranial generalization. No signs of recurrence are observed in the group of patients with primary ES of the skull base.

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All the 9 ES cases were microscopically represented by a tumor consisting of small round cells of regular shape containing round or oval nuclei with the high nucleus–cytoplasm ratio separated by fibrous interlayers. Chromatin dispersion embedded in karyons imparts them the characteristic “mirror-like” appearance. The mitotic activity in ES cells was low in all patients. Well-pronounced necrosis of tumor tissue was detected in 2 patients with primary ES and 3 patients with secondary ES. The features of tumor morphology (almost in all patients) made it difficult to diagnose ES only according to the morphology; differential diagnostics with other small cell malignant cells (neuroblastoma, rhabdo- and leiomyosarcoma, lymphoma, etc.) were required.

In all the cases, tumor cells expressed CD99 (p30/32MIC2) surface marker and vimentin on the membranes (Fig. 3). No expression of other markers (CD45, Desmin, Synaptophisin, Myogenin, Pan-Cytokeratin, etc.) was detected in tumor cells.

A FISH analysis has revealed translocation between chromosomes 11 and 22 [t(11;22) (q24;q12)] in 90–95% of tumor cells, which is a pathognomonic sign of ES (Fig. 4).

Table 3. Clinical presentation in patients with ES of the skull base

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General brain lesion symptoms (headache, nausea, vomiting, optic disc edema)</td>
<td>2</td>
</tr>
<tr>
<td>Skull swelling</td>
<td>2</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
</tr>
<tr>
<td>Ocular motility disorders</td>
<td>4</td>
</tr>
<tr>
<td>Visual loss (to complete blindness)</td>
<td>1</td>
</tr>
<tr>
<td>Occipital condyle syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Jugular foramen syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Facial and auditory nerves</td>
<td>4</td>
</tr>
<tr>
<td>Trigeminal nerve</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig. 3. Immunohistochemistry study: tumor cells express the CD99 (p30/32MIC2) surface marker on the cells.
Fig. 4. FISH study: translocation between chromosomes 11 and 12 typical of ES is determined.

Discussion

ES occurs in patients younger than 20 years of age in 90% of cases; the highest incidence rate is observed in 5–13-year-old patients [8]. The number of reported ES cases in older patients is rather small. In a series of 14 observations described by K. Desai et al. [13], the youngest patient was 18 months of age, while the oldest one was 40 years old. The mean age of patients was 14.5 years; in most cases, the disease onset was recorded at the age younger than 30 years. A single case of ES of the skull base in a 54-year-old patient was reported in literature.

The disease prevailed in male patients. According to the published data [8], the male : female ratio is 1.6:1–1.8:1. In our observation series, the male : female ratio was 1.2:1.

Primary ES is more likely to affect long bone shafts (47%), pelvic bones (29%), ribs and vertebrae (12%). Skull lesions in patients with ES is observed in 6–9% of cases. The tumor is more likely to affect the frontal and parietal bones. Temporal squama and mastoid bone, ethmoid bone, eye socket, and petrous temporal bone are involved in the pathological process less frequently [1, 3, 7, 9].

Sporadic cases of skull base lesions (involving both the primary ES and its metastases) were reported. A total of 36 cases of primary ES of the cranium have been reported since the early XX century. Among them, the skull base lesion was reported in 13 (36.1%) of cases [13]. In this group, the lesions of the petrous temporal bone was observed in 6 cases; eye socket, in 4 cases; mastoid bone, in 2 cases; and ethmoid bone, in 1 case [13].

ES is prone to develop metastases. In 75–80% of cases, the metastases manifest themselves during the first two years after the primary tumor had been detected. They are more likely to affect lungs (57%) and bones (34%) [24, 28]. Metastases to the CNS develop in 10–37% of cases [5, 13]. A. Colak et al. [5] reported on 16% of cases of metastases to the CNS (most of the metastases had spinal localization). A. Kulick and J. Mones [15] reported on 32% of cases of CNS lesion and mentioned that cerebral manifestation is typically observed within the first 2 years in 90% of patients.

A comprehensive diagnostic strategy is used in patients with ES of the skull base. Past medical history plays the key role in differential diagnosis between the primary and metastatic ES [4]. In all the observations of metastatic lesions of the skull that have been reported, the medical history contained the data that the patient had had some organs affected with ES and had received treatment [5].

There are no pathognomonic X-ray signs that enable one to differentiate between the primary and metastatic ES [6]. Cranigraphy and CT bone window photography of the skull revealed bone destruction [10]. Virtually no "onion skin" sign (which is roentgenologically typical of ES of long bones) has been observed in patients with skull lesion [10, 11].

According to the MRI data, tumors predominantly have a heterogeneous polynodal structure, contain multiple cysts, hemorrhagic and necrotic foci. The tissue shows hyperintensity with respect to brain and hypointensity with respect to the liquor in the T2-weighed image, while showing hypointensity with respect to brain and hyperintensity with respect to the liquor in the T1-weighed images. The tumor intensely accumulates the contrast agent when performing MRI with intravenous contrast [23].

The clinical presentation depends on localization and degree of tumor spread; its specificity remains the same regardless of the fact whether the tumor is primary or metastatic [5, 6]. According to the published data [11, 13], while headache (100%), increased intracranial pressure (75%), and skull swelling are the main symptoms in patients with convexital localization of the tumor, the clinical presentation mostly includes lesion of the cranial nerves in patients with tumor of the skull base. Lesion of the petrous temporal bone is characterized by facial nerve paralysis and hearing impairment. Tumor localization in the cuneiform bone causes ocular motility disorders and disturbance of the trigeminal nerve. Lesion of the caudal nerves is observed rarely, when the tumor localizes in the posterior cranial fossa and affects the occipital condyle [24].

The exact diagnosis is arrived at according to the data obtained by pathomorphological examination verified by the results of immunohistochemistry and genetic testing [16].

The differential diagnostic procedure should be performed using intracranial tumors with round cells, such as primitive neuroectodermal tumor, rhabdomyosarcoma, metastatic neuroblastoma, and lymphomas [10, 22].

Round cells arranged in the form of solid strata, minimal amount of cytoplasm, protruding nuclei, no rosette formation, mitoses, and the presence of bone structures
are the characteristic histological signs of ES [13]. Patient’s age and tumor localization facilitate diagnosis. Immunohistochemistry testing reveals vimentin and CD99 expression with the characteristic membrane staining [19]. The tests show negative results for the expression of desmin, S-100 protein, chromogranin (neuronal marker), lymphoid markers CD20 and CD3. ES differs from neuroblastoma, rhabdomyosarcoma, lymphoma, etc. by the absence of expression of synaptophysin, desmin, leukocyte antigen, and other markers [12, 18].

The immunohistochemistry and FISH studies, which determine translocation [(t(11; 22) (q24; q12)] that is typical of ES, are diagnostic and important prognostic factors [12, 16].

The immunohistochemistry test allows one to refine the tumor type: CD99 protein expression was observed in all cases [2, 17].

It is important that primary and metastatic tumors are virtually identical in terms of immunohistochemical parameters: the same proteins were expressed in both groups [15, 16].

However, there were some indirect factors that made the primary tumors differ from the metastatic ones. The Ki-67 labeling index was higher in patients with metastatic tumors and the number of mitoses was greater, which correlates with the more aggressive and malignant tumor growth and shorter life expectancies of patients as compared to the group of patients with primary ES [12, 16].

The combined treatment for both primary and metastatic ES is currently considered to be the optimal treatment method [21].

The aim of a surgical intervention is to reduce the tumor size as much as possible. In 14 observations with primary ES of the skull described by K. Desai et al. [13] in 2000, subtotal and total removal of the tumor was performed in 9 and 5 cases, respectively. A relapse was observed in only one patient after the total resection of the tumor. Hence, tumor resection should be as radical as possible within the admissible safety limits [6].

The choice for surgical approach is mostly determined by tumor localization. While only transcranial approach can be used in patients with convexital lesions, endoscopic transnasal interventions can be performed in patients with tumors of the skull base (in particular, if the chiasm-sellar region is affected) [21].

Treatment of ES is multimodal; it comprises the maximum resection of the tumor followed by radiation and chemotherapy [1, 24].

Radiation therapy is used after surgical interventions as an adjuvant method for patients with primary and metastatic tumors. The recommended scheme for radiation therapy is 1.5–2 Gy/day, 5 days per week, TBD 40–50 Gy [12].

The prognosis for patients with ES used to be unfavorable when surgical intervention and radiation therapy were the only treatment options; the 5-year survival rate was less than 8–15% [8]. In 1974, the combination of postoperative multimodal chemotherapy and radiation therapy was implemented by Rosen. The 5-year survival rate increased from 10 to 55–60%. The round cell therapy (RCT) I, which consisted of 6 cycles of cisplatin and etoposide, vincristin, doxorubicin and cyclophosphamide prescribed at a 3-week interval was used until 1990. The chemotherapy was followed by radiation therapy with TBD 40–50 Gy. When the RCT-I option was used, the 5-year survival rate was 20%. The RCT-II protocol has been used since 1993, which increased the 5-year survival rate to 50%. This protocol consists of the induction phase comprising two cycles of iodophosphamide and etoposide, vincristin, doxorubicin, and cyclophosphamide prescribed at 3-week intervals. Radiation therapy with TBD 40–50 Gy is used 8–9 weeks after the induction therapy had been completed. The supportive chemotherapy consists of 6 cycles of vincristin, doxorubicin, cyclophosphamide, and daunomycin; it is further prescribed at 3-week intervals [1, 14, 25].

The presence of distant metastases by the time of diagnosis is the most unfavorable prognostic factor in patients with ES [26]. The other unfavorable factors include patient’s age older than 10 years; tumor size larger than 200 ml; “median” localization (e.g., of the pelvis and spine), low efficiency of chemotherapy [14].

The treatment outcomes in patients with ES become better with time. According to Mayo Clinic reports, the 5-year survival rate during the period from 1950 to 1968 was as low as 21.8% [15, 23]. According to the reports in 2000, the 5-year survival rate in patients with ES in the same hospital reached 74%. The 50–80% 2-year survival rate without any signs of the disease after the complex therapy was reported in another large series of observations [14].

The primary ES of the skull base has a more favorable course as compared to the metastatic tumor. Among 14 patients, 8 (57.1%) ones survived five years. It is a good outcome as compared to the literature data. The patients with cranial metastases usually do not survive five years, regardless of the therapy options [1].

Conclusions

Both metastatic and primary ES of the skull base occur with almost identical frequencies. The primary tumors are typical of patients younger than 3 years, while the metastatic tumors are observed in patients older than 11 years. There is past medical history of primary tumor in all cases of metastases to the skull base. The clinical presentation usually consists of the symptoms of cranial nerve lesions. There are no pathognomonic X-ray signs that enable one to differentiate between the primary and metastatic ES. The higher Ki-67 labeling index is the only difference when conducting a pathomorphology test. Combined treatment for both the primary and metastatic tumors is applied according to the same scheme and allows one to achieve relatively good outcomes. The prognosis is more favorable in patients with primary ES.
ORGANIC ARTICLES

REFERENCES


Commentary

While being the second most frequent malignant bone cancer, Ewing’s sarcoma (ES) affects skull bones in 9% of cases. It is a relatively rare tumor in neurosurgical practice. The data in literature devoted to ES of the skull mostly include the description of sporadic cases. ES is known to have a rather aggressive course and to be manifested multicentrically in 30% of cases.

This study is of significant interest due to the fact that it presents a thorough comparative analysis of the metastatic and primary ES of the skull base in patients operated on in the same hospital. It is a part of the problem of skull base surgery. Despite the advance in modern neurosurgery, it is not radically removal of tumors of the skull base is not always feasible.

The authors have analyzed 9 cases of ES of the skull base who were operated in the Burdenko Neurosurgical Institute. The tumor was primary in 5 cases and was of metastatic origin in 4 cases.

The problem of differential diagnosis of the primary and metastatic ES of the central nervous system is rather topical from the perspective of disease prognosis, since the prognosis in patients with metastatic ES to the CNS is known to be unfavorable using any treatment methods and the life expectancy of patients is less than 5 years. In patients with primary ES, the use of radiation therapy combined with polychemotherapy enables one to increase the life expectancy of patients by over 5 years.

The tumor pathomorphology was thoroughly described in this study. The authors compared the morphological, immuno- histochemical, and genetic presentations of the primary and metastatic tumors and showed them to be identical. No differences between these two groups have been detected, which attests to the identical genetic and pathomorphological bases of the tumors, on one hand, and substantiates that the same treatment regimen can be used, on the other hand. The identical treatment strategy was used: the possibly complete radical removal of the tumor followed by radiation- and chemotherapy was performed. Of course, the aspects of the surgical strategy (how to obtain the maximum reduction of tumor size) are of the most significant interest for neurosurgeons. In patients with ES, the possibly complete radical removal of the tumor is the key criterion for successful treatment. However, with allowance for the not very favorable prognosis for patients with metastatic lesions, surgeons should not seek the “invalidizing” radicality that results only in “treating the tomography scans”. The radiosurgical techniques should presumably be emphasized in these cases.

G.G. Shaginyan (Moscow)

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Osteochondrosis of the cervical spine occurs predominantly in patients belonging to the 35–60-year age group, ranking second after lumbar osteochondrosis [4, 5]. Deformity of the spinal channel, spinal cord compression, overdistension or squeezing of vertebral vessels in the deformed vertebral foramina, and instability of functional spinal units (FSU) can cause compression of the spinal cord or/and its rootlets. Taking into account the anatomo-physiological features of this spinal segment, the existence of pathological compression is associated with a high risk of development of myelopathy with different severity of neurological symptoms, which significantly deteriorates quality of life and causes disability if not timely treated [4, 5, 7, 9]. This pathological process in the cervical spine is an indication for surgical treatment [1, 4, 7].

The surgical management is aimed at eliminating the compression of the spinal cord and/or spinal cord rootlets and stabilizing the functional spinal unit [1, 8, 29, 33]. Anterior cervical discectomy with fixation using an iliac crest autograft has been proven to be an effective method for treating radiculopathy and myelopathy after cervical fusion. Nevertheless, the development of complications in a donor region in up to 22% of patients has been reported in [13]. A number of alternative materials for spinal fusion have been proposed in order to avoid these complications: homografts, xenografts, demineralized bone matrix, and cages. The materials currently used for interbody fusion include bone autograft; stand-alone titanium, carbon, and PEEK cages; cage with plate; and combined plate cage implants. There is no unanimous opinion on whether it is reasonable to use plates to ensure additional fixation of a segment stabilized with a cage or not. A number of authors believe [26] that the additional use of a plate for single- and double-level cervical fusion in patients with degenerative diseases of the cervical spine can improve vertebral fusion, reduce the frequency of spinal subsidence and complications, eventually improving the clinical outcomes. P. Fernandes et al. [17] used a computer model of fusion at the C5–C6 disc level to demonstrate that the addition of an anterior cervical plate to a cage results in redistribution of tissue strain and reduces its value on each individual graft. Nevertheless, a number of authors [2, 18, 27] have achieved good results using stand-alone cages without any additional fixation with a plate. Another interesting technical solution — plate-cage combination — has its advocates as well [1, 12, 20–22, 24, 32]. The titanium PCB plate cage (Plate cage Benezech) was named after the French inventor who designed it in 1996. PCB is a titanium graft that has been proposed as an alternative to bone autograft to ensure fixation of the adjacent bodies of cervical vertebrae. PCB is a combination of a cage with anatomical shape and an asymmetric plate, which allows one to perform fixation at the adjacent levels, in a single graft.
Cages and plates have conventionally been manufactured from titanium (Ti). PEEK is a relatively new material that has recently been used to manufacture cages.

PEEK (polyether ether ketone) is a transparent non-opaque semicrystalline thermoplastic polymer exhibiting various mechanical properties and high chemical resistance. The Young’s modulus of PEEK is 3.6 GPa (for the sake of comparison, the Young’s modulus of titanium is 105–120 GPa; a bone exhibits anisotropy within a broad range: from 0.09–0.8 GPa for vertebral cancellous tissue to 10–20 GPa for cortical tissue [16, 31]). PEEK has high resistance against thermal degradation and impact of the organic environment; it is a biocompatible, non-absorbable, noncytotoxic, and non-mutagenic material [34]. The biomechanical indicators and the elasticity coefficient of PEEK are similar to those of bone tissue; thus, PEEK cages enhance the frequency of fusion of the adjacent vertebra and facilitate bone density conservation in the adjacent vertebrae. The non-opacity of these cages makes it possible to assess the osteointegration condition radiographically.

In 2007, an integrated graft consisting of a titanium plate and a polymeric cage and named PCB Evolution by the manufacturer was designed; this graft combines the advantages of PEEK as a material and those of the PCB device. It contains two X-ray contrast labels to verify cage position. Some experience and good results have been obtained for the individual use of PEEK cages and plates in patients with traumatic and degenerative lesions of the cervical spine. No data on using the combined plate cage groups under endotracheal anesthesia. The first stage comprised microsurgical decompression by discectomy and resection of posterior exostosis using an Olympus 5000 surgical microscope and the conventional microsurgery instrument set (Aesculap, Germany). A rectangular-shaped incision in the anterior portion of the fibrous ring was performed with a scalpel; the degenerated disc was removed using curettes and forceps until closing plates were reached. Microsurgical decompression of the dural sac and roots via the removal of the herniated disc or resection of posterior osteophytes from the central and lateral channels was performed using a high-speed drill and a diamond cutter set. At the second stage, the cage height was determined, the graft of a required size was implanted using a support and fixed across its diagonal into the bodies of the adjacent vertebrae using two screws. All the stabilization stages were controlled radiographically using a Siemens Arcadis electro-optical transducer. In all the patients, external immobilization with a semi-rigid collar was performed before the postanesthetic recovery.

Materials and Methods

The treatment outcomes in 34 patients (15 females, 19 males) aged 18–62 years (mean age 32.4 years) with compression of the spinal cord and/or its rootlets by disc osteophyte complexes, to whom 37 hybrid PCB Evolution plate cage (Scient’x, France) had been implanted, were analyzed. All the patients were operated on during the period between 2008 and 2010 at the Neurosurgery Department of the Railway Clinical Hospital (Irkutsk–Passenger Station) and at the Neurosurgery Department of the Scientific Center of Reconstructive and Restorative Surgery, SB RAS.

Patient complaints, medical history, and neurological status were assessed during the preoperative period. Patients underwent general physical and instrumental examination; the neck disability index (NDI) was also determined. Pain intensity during the pre- and postoperative periods was evaluated using the visual analogue pain scale (VAPS). The Nurick scale and MacNab criteria [28, 30] were used to assess the efficiency of outcomes after surgical treatment. Furthermore, surgery duration, blood loss volume, length of postoperative bed rest, and duration of hospital stay were determined.

Standard spondylography supplemented with functional probes (in 34 patients), magnetic resonance imaging (MRI) (in 23 patients), multispiral computed tomography (MSCT) (in 11 patients), and upper extremity electroneuromyography (ENMG) (in 32 patients) were conducted to verify the affected functional spinal unit.

All the patients with disc–radicular conflict underwent conventional conservative treatment for 6–12 weeks before the surgery, which turned out to be not efficient enough.

C5–C6 was the spine segment most frequently affected by the pathological process (Fig. 1). The surgery was performed at a single level in 31 (91%) patients and at two adjacent levels in 3 (9%) patients.

The study results were statistically processed on a PC using database processing software Microsoft Excel and Statistica 6.0. Nonparametric statistical criteria were used to assess the significance of differences between the samples; the level $p<0.05$ was used as the lower limit of the confidence interval [3, 6].

Surgical tactics. Left-sided parapharyngeal approach to the anterior surface of the vertebral column according to Cloward was performed in all patients in the analyzed group under endotracheal anesthesia. The first stage comprised microsurgical decompression by discectomy and resection of posterior exostosis using an Olympus 5000 surgical microscope and the conventional microsurgery instrument set (Aesculap, Germany). A rectangular-shaped incision in the anterior portion of the fibrous ring was performed with a scalpel; the degenerated disc was removed using curettes and forceps until closing plates were reached. Microsurgical decompression of the dural sac and rootlets via the removal of the herniated disc or resection of posterior osteophytes from the central and lateral channels was performed using a high-speed drill and a diamond cutter set. At the second stage, the cage height was determined, the graft of a required size was implanted using a support and fixed across its diagonal into the bodies of the adjacent vertebrae using two screws. All the stabilization stages were controlled radiographically using a Siemens Arcadis electro-optical transducer. In all the patients, external immobilization with a semi-rigid collar was performed before the postanesthetic recovery.

Results

The following values were determined by analyzing the outcomes of surgical treatment: surgery duration varied from 80 to 120 min (median value – 92 min); volume of blood loss varied from 35 to 75 ml (median value – 50 ml); patients became active on day 2; the number of bed-days after the surgery varied from 7 to 9 (median value – 8).
A significant pain relief both in the cervical spine and the upper limbs was observed after the surgery. The evaluation based on VAPS (Fig. 2, a) revealed the positive dynamics consisting in reduction of pain intensity in the cervical spine from 47 to 22 and reduction of pain intensity in the upper limb (see Fig. 2, b) from 58 to 23 ($p<0.05$).

The evaluation of the neck disability index (NDI) revealed the positive dynamics during the first three months after the surgery, namely, a change in NDI from 48 to 27. The NDI remained at the specified level during the follow-up period (Fig. 3).

The evaluation according to the Nurick scale demonstrated that the complete relief of neurological symptoms was observed in 17 (30%) patients; improvement — in 14 (41%); condition unchanged — in 2 (6%); neurological deterioration — in 1 (3%).

According to the subjective evaluation based on the MacNab criteria, the postoperative outcomes were distributed in the following manner: excellent — in 15 (44%), good — in 14 (41%), fair — in 4 (12%), and dissatisfactory — in 1 (3%) patient.

An analysis of the outcomes of surgical treatment during follow-up examination after the conventional periods of time has demonstrated that a complete stable regression of sensitivity and motion disorders took place in all the patients after the surgery.

An analysis of work rehabilitation has demonstrated that among all the patients operated on, 10 patients (29%) returned to their former workplace 2 months after surgery; 12 patients (35%) changed their occupation to an easier one after 2 months; 8 patients (24%) became capable of working 6 months after surgical treatment; and 4 patients (12%) of retirement age returned to their usual lifestyle 6 months after the surgery.

During the postoperative period, 23 (68%) patients underwent MRI or MSCT control during the period of 2–18 months (8.2 months on average); no data on the recurrence of disc radicular or discomedullary conflict have been obtained; the condition of devices was satisfactory. Rigid fixation was achieved in all the patients after the surgery.

A comparative analysis of neurophysiological ENMG indicators during the postoperative period has demonstrated that during the period from 3 to 18 months, the recovery of impulse conduction along the neural structures that used to be compressed took place in 26 patients (75%) who had been operated on.

A single complication (improper graft position owing to loosening of the upper screw of the plate in the hybrid cage) has been observed. Taking into account the absence of complaints, neurological deficit, radiographic indicators of instability of the operated unit and endoscopic indicators of esophageal compression, a decision was made that no repeated surgical intervention was required.

**Clinical example.** A female patient T., diagnosed with osteochondrosis of the cervical spine was admitted to the Neurosurgery Department of the Railway Clinical Hospital at Irkutsk–Passenger Station. Herniated C5–C6, C6–C7 discs. Radiculoneuritis in C6, C7 (on the right side) with moderate distal arm paresis. The pronounced muscular tonic syndrome. Chronic recurrent course. The aggravation stage.

The patient complained of intense pain in the cervical spine that increased under dynamic load and radiated in the supraclavicular area, in the right shoulder blade, in the right shoulder (along its outer side), and in the forearm; as well as of the “insect-crawling sensation”, of numbness in the pain area, and of weakness in the right hand. It was found from the past history that the patient suffered from pain in the cervical spine throughout a year after exposure to cold. The pain syndrome was aggravated six months earlier; pain started to radiate in the right arm. The patient used self-care; the effect was insignificant. The last exacerbation started 2 weeks before the admission.

A neurological examination has revealed that the motion in the cervical spine was painful and limited when the patient bent forward or rightward. Pain during the palpation of the C5–C7 spinous process and grade 2 or 3 strain of paravertebral muscles. Brisk biceps reflex D=S; brisk triceps reflex D=S; brisk carpopedal reflex D<S. Brisk patellar (D=S) and the Achilles (D=S) reflexes. No pathological reflexes detected. The presence of tenor hypotonia. Hand grip strength score: D – 3, S – 5; leg strength score – 5. Hypoesthesia in C6 and C7 dermatomes. No pelvic pathologies were observed.

The results of instrumental examination were as follows: radiography of the cervical spine (Fig. 4); osteochondrosis of the cervical spine. Kyphosis at the level of C5–C6. Radiography of the cervical spine with functional probes (see Fig. 4): limited flexion and extension with instability in the functional spinal units C5–C6, C6–C7. MRI of the cervical spine (Fig. 5): osteochondrosis of the cervical spine. Herniated C5–C6, C6–C7 discs. Upper
limb ENMG: impaired conduction through the C6, C7 rootlets on the right side (indicators of axonopathy).

The patient underwent microsurgical removal of the hernia in C5–C6, C6–C7 discs through an anterior parapharyngeal approach and foraminotomy along the C6 and C7 rootlets on the right side. Anterior fusion of C5–C6, C6–C7 with a PCB Evolution hybrid titanium plate cage was performed.

After treating the operative field with an antiseptic, an incision on the left side, along the medial margin of the digging muscle was performed in the patient under endotracheal anesthesia. The typical left-side parapharyngeal approach to the anterior margin of the C5, C6, and C7 bodies was performed without any technical difficulties. The radiographic control with verification of the lesion level was conducted. Microdiscectomy was performed using a high-speed drill and supplemented with microsurgical removal of the posterior exostoses of the C5, C6, C7 bodies and foraminotomy for the C6, C7 rootlets on the right side. Anterior fusion of C5–C6, C6–C7 was performed using PCB Evolution plate cages. The dimensions of a plate cage (moderate distraction of C5–C6): 6.5 mm 11PCBH 65 (correction of the kyphotic deformity); dimensions of the plate cage for C6–C7: 5.5 mm 11PCBH 55. The plates of the cages were fixed on the C5, C6, and C7 using the original 12-mm long screws. Radiographic control: proper position of the plates, screws, and cages. Hemostasis. Layered closure of the surgical wound. Aseptic dressing. External fixation of the cervical spine using a Philadelphia collar.

The patient underwent postoperative examination. Radiography of the cervical spine (Fig. 6) detected no destruction of bone tissue around the titanium units. The kyphotic deformity at the C5–C6 level was eliminated.

The data of postoperative MRI of the cervical spine (Fig. 7): osteochondrosis of the cervical segment of the vertebral column, period 2–3. Condition after spinal decompression and stabilizing reconstructive surgery at the C5–C7 level.

Patient's condition at discharge was satisfactory; sutures were removed 8 days after the surgery; wound healing by primary intention. The unbiased clinical neurological examination and evaluation using VAPS, Nurick, and MacNab scales have demonstrated complete regression of neurological disorders; no weakness in the right hand was detected.

The patient returned to her workplace (a fitness instructor) 6 weeks after the surgery. Upper limb ENMG during stimulation myography of the right upper extremity has revealed no significant changes in the peripheral nerves (after 1.5 months). No recurrent pain syndrome and pathological neurological signs have been detected during the follow-up control examination after 3, 6, and 12 months. After 16 months, the clinical and neurological examination, neuroimaging, and neurophysiology data correspond to the normal condition.

Discussion

We support the opinion of a number of authors [2, 14, 27] that the anterior cervical discectomy with fixation using a stand-alone cage and the conventional autograft fixation demonstrate similarly good results in terms of the achieved fusion, stability, and maintenance of the disc height. On the other hand, we also support the au-
The authors [11, 15, 18] who have reported on the cases of cage subsidence and loss of lordosis when the cages were not fixed with a plate. A decrease in the contact surface area between the end plates and the cage increase instability and the problems associated with it [25]. Subsidence is a common phenomenon in spinal surgery, which develops as a result of improper contact between a cage or a graft and the bone tissue. Significant subsidence can cause such adverse effects as segmental kyphosis, foraminal stenosis with the recurrence of radiculopathy and neck pain. A biomechanical study carried out by J. Hakalo et al. [19] has demonstrated that the subsidence of cervical vertebrae at the intervention spot is more likely to occur when a stand-alone cage (in particular, one having a cylindrical shape and small dimensions) is used for stabilization as compared to fusion using a cage additionally fixed with a plate.

The resulting clinical results are comparable to the data of the other publications where the cervical level fusion was analyzed (see Table).

We have not encountered such complications as dysphagia or subsidence of the adjacent vertebrae. The segments stabilized using PEEK material imitate well the intact physiological load at the adjacent levels, which may reduce the probability of degeneration at the adjacent levels. No complications of this type have been observed during the long-term follow-up period among 23 (68%) patients who underwent control MRI or MSCT examination.

The assessment of pain syndrome according to the VAPS scale has shown no fundamental differences from the series reported in literature. The results are indicative of completeness and adequacy of the surgical treatment selected.
The advantage of using the hybrid plate cage is its simple design with the minimum number of surgical instruments required for the implantation; the possibility to ensure the immediate rigid interbody stabilization of the operated functional spinal unit (so that there is no need to wear the collar for a long period after the surgery), feasibility of stabilization at two or more injured levels (the diagonal arrangement of stabilizing plates). The use of the PEEK material has not revealed any negative aspects and has not result in any complications. The relative drawbacks of this device were associated with the problems of combining the microsurgical instruments when implanting the cages (long instrument handles); an insufficiently broad range of the size of grafts and fixing screws; and no opportunity to combine them with a number of other devices.

**Conclusions**

Surgical treatment in patients with disc-radicular and discomedullary conflict at the cervical level, involving the implantation of a hybrid plate cage made of a titanium plate and a PEEK cage, provided good clinical and functional short- and long-term outcomes. When
properly performed, anterior cervical interbody fusion using a PCB Evolution plate cage is a simple and effective method with a low complication rate. Further research is required to study the biomechanical features of the operated spinal segment, bone tissue response, and the functional effect of the PEEK component combined with the titanium plate of the plate cage, in particular on the adjacent FSU.

### Comparison of the outcomes of cervical fusion

<table>
<thead>
<tr>
<th>Author</th>
<th>Cervical fusion technique, abs.</th>
<th>Excellent/ good outcome, scale: abs. (%)</th>
<th>VAPS before/after</th>
<th>NDI before/after</th>
<th>Complications, abs. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autobone + plate (23)</td>
<td>—</td>
<td>—</td>
<td>21/9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cage + plate (38)</td>
<td>—</td>
<td>—</td>
<td>20/10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cage (44)</td>
<td></td>
<td></td>
<td>23/11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A total of 30 (23 traumatic + 7 degenerative)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyung Jin Song et al., 2010 [26]</td>
<td>PEEK cage filled with autobone + Ti plate</td>
<td>76 (91)</td>
<td>—</td>
<td>—</td>
<td>4 (4.8) – transient dysphagia 8 (9.6) – subsidence, including 1 – reoperation</td>
</tr>
<tr>
<td>E. Gerecek et al., 2003 [18]</td>
<td>Ti cage filled with autobone</td>
<td>7 (87)</td>
<td>—</td>
<td>—</td>
<td>1 (12.5) – symptomatic subsidence, foraminal stenosis; 5 (55.5) – asymptotic subsidence</td>
</tr>
<tr>
<td>J. Liao et al., 2008 [27]</td>
<td>PEEK cage</td>
<td>14 (74)</td>
<td>—</td>
<td>—</td>
<td>?</td>
</tr>
<tr>
<td>G. Samandouras et al., 2001 [32]</td>
<td>PCB Ti plate cage</td>
<td>27 (93)</td>
<td>—</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>B. Walchli, 2000 [22]</td>
<td>PCB Ti plate cage</td>
<td>Odom: 15 (75)</td>
<td>77/24</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Kyung Jin Song et al., 2011 [25]</td>
<td>PEEK cage (three-level)</td>
<td>—</td>
<td>—</td>
<td>55/24</td>
<td>3 (14.3) – asymptomatic degenerative changes at the adjacent levels; 3 (14.3) – asymptomatic screw loosening; 5 (23.8) – cage subsidence</td>
</tr>
<tr>
<td>G. Matge, T. Leclercq, 2000 [29]</td>
<td>Ti cage</td>
<td>98 (72)</td>
<td>—</td>
<td>—</td>
<td>?</td>
</tr>
<tr>
<td>M. Akula et al., 2008 [10]</td>
<td>PCB Ti plate cage</td>
<td>Prolo: 43 (86)</td>
<td>66/17</td>
<td>—</td>
<td>?</td>
</tr>
<tr>
<td>Our data</td>
<td>Hybrid PCB Evolution plate (Ti) cage (PEEK)</td>
<td>Nurick: 31 (91)</td>
<td>58/23</td>
<td>48/27</td>
<td>1 (2,9) – asymptomatic screw loosening</td>
</tr>
</tbody>
</table>
The evolution of the development of single-level cervical fusion has recently acquired a trend towards combining an interbody graft with a cervical plate. Stand-alone interbody grafts made of titanium, carbon, or PEEK were fixed between the vertebral bodies by wedging only; hence, there was a probability of graft migration. The implantation of a larger interbody graft with a cervical plate can be considered as an alternative to autologous bone graft in the treatment of cervical spondylosis.

The clinical results are in agreement with the data obtained in the other studies. The article can be useful for spinal surgeons and other medical practitioners dealing with the treatment of disorders of the cervical spine.

The present article is devoted to the analysis of clinical outcomes of anterior cervical fusion using a PCB interbody graft. Let us note that the primary goal of a surgeon is to perform adequate decompression of neural structures. Various methods can be used to perform fusion. We consider the aforedescribed (hybrid) interbody graft to be the most advanced and reliable construct to be used during a single-level fusion. In order to ensure interbody fusion, it is recommended that PCB is placed into a cavity of the interbody graft. One should also mention the advantages of PEEK material as compared to titanium or carbon, since this material imitates well the physiological load on the adjacent levels, which can reduce the probability of degeneration at the adjacent levels.

In general, this article describes the modern cervical surgical techniques and analyzes 34 operated patients with this pathology, to whom 37 interbody grafts have been implanted. The clinical results are in agreement with the data obtained in the other studies. The article can be useful for spinal surgeons and other medical practitioners dealing with the treatment of spine pathologies.

N.A. Konovalov (Moscow)
Cerebral amyloid angiopathy (CAA; also known as congophilic angiopathy or senile amyloid angiopathy) is a specific progressive microangiopathy characterized by extracellular deposition of amorphous strongly eosinophilic compounds on the walls of small and middle-sized cerebral arteries with a high risk of blood vessel rupture [5, 16, 24, 28, 43]. Microaneurysms in the walls of blood vessels caused by secondary fibrinogenous necrosis can also be a reason for hemorrhages [14, 31, 38, 39]. Gray substance was found to be predominantly affected, while no signs of systemic amyloidosis were observed [23, 25, 30, 37, 40, 41]. Because of the selective lesioning of the cortex and pia arteries, the hemorrhages in patients with CAA mostly have the peripheral and lobar (subcortical) localization. Among all non-traumatic intracerebral hemorrhages, the frequency of hematomas associated with CAA is 5.4–10% [4, 5, 21]. The hematomas most typically localize in the frontal, parietal, and occipital lobes [22, 26, 33, 34]. Hematomas in patients with CAA are characterized by recurrence tendency; the localization and side of subsequent hemorrhage are different [29, 32, 33, 37].

No pathognomonic clinical signs have been described for CAA. In case of mild petechial hemorrhage, progression of CAA can clinically asymptomat [9, 22, 27, 34]. In the overwhelming majority of patients with CAA, the clinically significant hemorrhages (in terms of their size) can be accompanied by the disruption of cognitive functioning, visual perception, abstract thinking, verbal memory, and speech [16, 29, 35, 36, 44]. Asymptomatic small-sized hemorrhages of small size that cannot be detected in the standard models of magnetic resonance imaging (MRI) can be detected in the “gradient–echo” mode, since this method amplifies the signal caused by deposition of iron-containing products [3, 5, 11, 16, 22, 37, 40].

The Boston criteria developed by S. Greenberg et al. [29] are the main tool to diagnose CAA. According to these criteria, no patients have been intra vitam diagnosed with “verified CAA”. The term “probable CAA” can be used in clinical practice for diagnosis formulation. Histological verification of CAA requires special techniques and equipment [28, 29, 36, 37], which are unfortunately unavailable at most treatment facilities.

Since CAA is currently considered to be an incurable (or, to be more specific, hardly curable) disease, only symptomatic treatment can be used [9, 21, 43]. The major aim of therapy is to prevent progressive dementia of the Alzheimer type [9, 24, 35]. If clinically indicated, surgical removal of hematomas caused by CAA is considered to be justified, since it has a favorable effect [16, 21].

Thus, CAA is a severe and almost incurable disease. It can hardly be diagnosed intra vitam and causes intracerebral hematomas that are unique in clinico-anatomical terms and have a rather unfavorable prognosis [38, 39, 41–43]. For the sake of comparison, it can be mentioned that peripheral neuropathy with primary amiloidosis is also an inevitably progressive and incurable disease [20].

In order to demonstrate the difficulties associated with diagnosis of CAA and selection of an adequate treatment strategy, let us present the medical history of one of the patients.

A 62-year-old male patient admitted to the neurological clinic after a stroke episode. The man complained of headache. His relatives reported the impairment of speech, memory loss, and behavioral changes. The onset of disease was rapid. In the morning, 20–30 min after the man woke up and while remaining in bed,
he complained of acute severe headache. The headache intensity subsided following the subsequent 2 h, but “an odd sensation in the head” was felt. Two hours later, the patient’s spouse has noticed speech impairment (disorganized speech). The patient was excited, had uncritical and aggressive behavior and negative attitude toward examination and hospitalization. The next morning he became more aggressive; no improvement of speech was observed. The patient was depressed and refused to take medication. In the evening, the coordination of the right limbs was suddenly impaired (which lasted for ~3–4 min). The patient was hospitalized to the department of neurosurgery in an ambulance car. Hemorrhagic stroke was diagnosed by multispiral computed tomography (MSCT) (Fig. 1). Patient’s condition improved to a certain extent after 1 week of conservative therapy. His family members initiated conducting MRI of the brain (Fig. 2); according to the results, the patient was placed in the neurosurgical clinic. The past medical history has shown that the man used to be a medical technician; did not suffer from hypertension; did not have alcohol problems; was a right-handed person.

The patient was admitted to hospital at a compensated condition. Pulse rate was regular, 80 bpm; blood pressure (BP) was 120/80 mm Hg. The man readily established verbal contact, understood speech addressed to him, showed little criticism, answered the questions (but the answers occasionally were deviously relevant). Dual disturbance of orientation perception was observed: chronognosis disorder and absurd verbal responses to questions about the current location of a patient. The cognitive deficit manifested itself as mnestic and neurodynamic dysfunction and speech impairment (paraphasia). The patient had a limited upward gaze with poor convergence. The tendon and periosteal reflexes of the right leg were brisk. When performing the modified Romberg’s test, the patient deviated to the right side. Bilateral Babinski reflexes were observed.

The ophthalmoscopy has revealed angiopathy of retinal vessels. EEG showed a slow-wave activity in the frontal brain regions, signs of irritative excitability of the brain cortex and a significant reduction in activation response. No paroxysmal activity was observed. Among concomitant diseases, the bilateral Kimmerle anomaly and chronic venous insufficiency of the right lower extremity with varix dilatation should be mentioned.

With allowance for the fact that the patient older than 60 years had a non-hypertonic hematoma of lobar localization without any other reasons for hemorrhage, a hypothesis of “probable” CAA has been put forward. Based on the past medical history, the most frequent factors inducing hemorrhage were eliminated: hypertension, alcohol intake, physical activity, and hot baths.

When discussing the treatment tactics and indications for surgery, attention was paid to the fact that the hematoma localized near the strategically important region of the dominant brain hemisphere (gyrus angularis) [1, 10, 17]. Moreover, allowance was made for the fact that temporal hematomas even of small volume (below 30 cm³) are associated with an increased risk of the development of brain dislocation (up to 75%) with the symptoms of brain stem lesions, as opposed to lobar and parieto-occipital hematoma of the same volume [6, 7, 12–14, 18]. Despite the hemorrhage volume of 40 cm³ and no signs of dislocations, the clinical and neuroimaging presentation suggested that the hematoma should be interpreted as “aggressive” one [7]. In this connection, the decision to remove hematoma was made. Based on the facilities of the clinic, additional examination to detect arteriovenous malformation (AVM) was postponed until the postoperative period.

The hematoma was removed on day 12 after the stroke. Craniotomy was performed in the left frontotemporal region. Cortico tomy (up to 1.5 cm incision) was performed in the front regions of the gyrus temporalis superior. The hematoma mainly consisted of bundles; its dense portion was covered with a tender capsule. The total hematoma volume was 40 cm³. Hemosiderin deposition on the white matter of the intracerebral wound was observed.

Speech has significantly improved during the postoperative period; it became more clear and meaningful.

Fig. 1. MSCT, day 1 after the disease onset. A series of axial sections. Intracerebral hematoma of the left temporal lobe.

Fig. 2. MRI, day 7 after the disease onset. A series of axial sections. Intracerebral hematoma of the left temporal lobe. Perifocal edema and compression of the ipsilateral ventricle.
The patient was able to form grammatically correct sentences and made fewer errors when spelling words. Memory improvement was observed. The answers to questions occasionally remained deviously relevant; the patient experienced euphoria. Six days after the surgery, the control MSCT showed that the bed of the removed hematoma was filled with liquor (Fig. 3). The patient was discharged from the hospital on day 10 after the surgery with an improvement in his condition.

In order to eliminate AVM or another source of hemorrhage, MSCT angiography was performed on day 18 after the surgery. A subcortical intracerebral hematoma of the right parietal area was detected. No AVM signs were observed in the areas of the resected and newly formed hematomas (Fig. 4). The second hemorrhage occurred presumably within the period of day 18–30 after the first stroke (day 6–18 after the surgery).

The hypothesis of CAA has been verified when it became clear that the patient with a secondary hemorrhage (i.e., caused by nonarterial hypertension) had a second lobar (subcortical) hemorrhage of different localization.

The subsequent diagnostic process was focused on refining the etiology of hemorrhage. Additional laboratory tests and consultations with the related experts made it possible to gradually reduce the range of presumable etiological and pathogenetic mechanisms of hemorrhages. The following diseases were sequentially eliminated: ischemic stroke with secondary hemorrhage, meningoencephalitis, blood diseases (hemophilia, hemorrhagic diathesis, aplastic anemy, thrombocytopenic purpura, etc.), cranioencebral injury, vascular malformation, brain tumor, and leucosis.

After the hypothesis of “probable” CAA has been substantiated, an explanatory conversation was carried out with the patient’s family regarding the nature of the disease, the severity of morphological changes in brain vessels, possible unfavorable complications and effects. The patient’s relatives abstained from the second surgical intervention. The measures and means for preventing vascular dementia were planned in collaboration with neurologists. A sequential therapy scheme was developed, including antihipoxants and antioxidants (Mexidol, Idenbone), neurotropic (Memantine) and metabolic drugs (glycine), neurometabolic stimulators (Cerebrolysin), anticholinesterase agents (Reminyl), dopaminomimetics (Piribedil), and nootropic agents (Lucetam) [2, 15, 17, 19].

1.5 months after the first stroke, the man suddenly complained of severe chest pain during the daytime. Two freezing episodes accompanied by twitching of his left eye were observed. The patient was hospitalized to the emergency neurology department. He was excited, aggressive and did not obey staff’s requests. The afore-described stroke repeated thrice. An MSCT was carried out. The patient received drug therapy.

The control MRI scan (recorded 2 months after the first hemorrhage) showed a region of pathogenic intensity in the right parietal lobe (6×2.8 cm, with a small area of perifocal edema causing the deformation of the adjacent convolutions) (Fig. 5). The chemical shift area (hemoglobin) was determined according to the focus contour. The contents of the region had a liquid structure with hyperintense T1 and T2 signal parameters (methemoglobin). A 6.6×2.2 cm lens-shaped region with clear non-uniform contours and signal parameters from the liquor was detected in the anterosuperior areas of the temporal lobe (left-hand side). No MRI signs characteristic of amyloid lesion of the brain have been detected using gradient echo MRI (Fig. 6).

With allowance for the unconvincing lysis of the second (non-operated) hematoma, the persistent neuropsychological dysfunction, and signs of compression of the right lateral ventricle, the patient’s relatives consented to surgery. The removal and drainage of the chronic intracerebral hematoma in the right temporal and parietal lobes was carried out. Craniotomy in the right parietotemporal region was performed. The dura mater of brain was tense and hardly transmitted pulsating...
intracerebral hemorrhages; 3) elimination of any other reasons for hemorrhage.

In our opinion, this case is interesting due to the following features: 1) hematomas of non-hypertension etiology; 2) hematomas affect the subcortical regions of individual convolutions (gyrus temporalis superior and gyrus supramarginalis); 3) unique configuration (geometry) of hematomas (cigar-shaped and broken kidney-shaped), which mitigates the dislocation effect; 4) acute onset and subacute course of the disease.

The lobar localization and side of the second hemorrhage have supported the proposition that the distribution of amyloid angiopathy in the brain is segmental [9, 22, 26, 28, 30].

The unusual configuration of “amyloid” hematomas (differing from the hypertonic ones), which copies the brain convolutions (gyrus temporalis superior and gyrus supramarginalis) are also of interest. The first hematoma was cigar-shaped (Fig. 8), while the second one had a broken kidney shape (Z-shaped) (Fig. 9). Due to its relatively high kinetic (hydrodynamic) energy, hypertension hematoma disintegrates the medullary substance

In this case report, the patient was initially diagnosed with “possible” CAA, while the grounds for claiming “probable” cerebral amyloid angiopathy were subsequently obtained. The “probable” CAA was diagnosed based on the Boston criteria: 1) patient is older than 60 years; 2) two sequential circumscribed lobar hemorrhages; 3) elimination of any other reasons for hemorrhage.

In our opinion, this case is interesting due to the following features: 1) hematomas of non-hypertension etiology; 2) hematomas affect the subcortical regions of individual convolutions (gyrus temporalis superior and gyrus supramarginalis); 3) unique configuration (geometry) of hematomas (cigar-shaped and broken kidney-shaped), which mitigates the dislocation effect; 4) acute onset and subacute course of the disease.

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Fig. 8. MSCT. A series of parasagittal reconstructions (a). MRI. Parasagittal section (b). The “cigar-shaped” configuration of the cerebral hematoma in the first temporal convolution.

(by disrupting tissues) [8], while the “amyloid hematoma” has relatively lower kinetic energy and “splits” or moves the tissues apart. It is probably due to these features that amyloid hematomas (as opposed to the calculated size) had a weaker mass effect and were characterized by subacute course.

Fig. 9. MRI. A series of parasagittal sections. The “broked kidney-shaped” (Z-shaped) configuration of amyloid hematoma.

In connection with the predicted increase in CAA prevalence, there is a demand for developing a number of provisions that would determine neurosurgeon’s attitude toward this problem. While we are well aware of the fact that a certain concept cannot be formed based on individual case reports, we would like to mention that in-depth clinical studies and specialized research are required to establish the attitude toward therapy strategy and choice of the surgical intervention method [4].

Conclusions

1. Intracerebral hematomas of amyloid origin may have a certain configuration copying the shape of the affected convolution according to its outline, which can be most clearly seen in sagittal and parasagittal sections, as well as in MRI and MSCT reconstructions.
2. Surgical treatment of hematomas caused by CAA can improve patient’s neuropsychological status.
3. Diagnosis of CAA in patients allows one to prevent the complications of this disease and to develop the treatment strategy at the time of manifestation and in the long-term period.

REFERENCES

Amyloid angiopathy has been known for a long time and hemorrhagic stroke remains one of the most frequent causes of death in older people. The incidence of amyloid angiopathy increases with age, and it is a frequent cause of brain hemorrhage. Amyloid angiopathy is a frequent cause of spontaneous brain hemorrhage and is associated with an increased risk of recurrent hemorrhage.

A case report of recurrent intracerebral hemorrhage with the formation of lobar hematoma in different regions of the cerebral hemispheres is presented. A thorough clinical analysis of the clinical course and sequential elimination of all possible reasons for the hemorrhage allowed the authors to draw a conclusion that amyloid angiopathy was the most probable reason.

Amyloid angiopathy has been known for a long time as the reason for macro- and microhemorrhage and dementia without hemorrhage in elderly patients; the significance of this pathology in the genesis of hemorrhage and dementia increases with age. Some researchers have reported that amyloid angiopathy ranks first among the reasons for hemorrhagic stroke in patients older than 70 years. In addition to the age-related features, bleedings in patients with amyloid angiopathy have a number of morphological and clinical features that make it possible to diagnose this pathology intra vitam with a high degree of probability. A thorough description and analysis of these features was presented in this study.
This study is valuable due to the fact that it focuses on amyloid angiopathy as a reason for the appreciably common clinical cerebral pathology, which provides further incentive to conducting research in this area. The analysis of the previously published data performed by the authors demonstrates that there are sporadic Russian publications devoted to this topic, while the genesis of hemorrhagic stroke is conventionally attributed to arterial hypertension in clinical studies. Meanwhile, as judged from English publications, both clinical and experimental studies focused on the development of amyloid angiopathy are being actively carried out. It has been demonstrated that beta-amyloid deposition on the walls of small cerebral vessels is caused by complex genetic and biochemical mechanisms regulating the synthesis of various amyloid proteins. The elucidation of these mechanisms will presumably allow one to design diagnostic markers of amyloid angiopathy and prevent both complications related to this pathology and the pathology itself in future. A reader will have a more clear idea on the advance in these studies if the authors have listed the available publications over the past 4 years.

The study also demonstrate an adequate methodological approach to refining the reason for intracranial hemorrhage, which consists in possibly accurate determining the cause of hemorrhage in each specific case, which eventually determines the strategy of therapy and disease prevention.

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Current Opinion on Craniopharyngioma Biology
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Over the recent years, a considerable number of studies devoted to craniopharyngioma morphology have been performed. Over 35 factors that could be related to the craniopharyngioma growth are known: Ki-67, p53, beta-catenin, p63, Retinoic acid receptors, Galectin-3, MIF, MVD, CK, etc. Despite such a variety of factors, none of them, except for Ki-67, strongly correlates with the risk of tumor recurrence and none can be associated with a particular tumor type. Most studies have focused on a very small number of factors and have been carried out in relatively small groups of patients. Most publications have been devoted to the Ki-67, beta-catenin and p53, and the largest number of patients enrolled in the study was 67. In this survey, we made an attempt to review the literature on craniopharyngioma biology and to identify further research areas to obtain data that could affect the choice of treatment and outcome of this complex disease.

Keywords: craniopharyngioma, biology, growth factors, Ki-67.

Abbreviations:

CP – craniopharyngioma
ACP – adamantinomatous craniopharyngioma
PCP – papillary craniopharyngioma
MVD – microvascular density
VEGF – vascular endothelial growth factor
MIF – macrophage-inhibiting factor
WNT (a combination of the Drosophila gene known as Wg (wingless) and the homologous vertebrate gene Int) – the name of a complex cascade of a large number of proteins that form the so-called signaling pathway participating in embryogenesis, tissue differentiation, and cancerogenesis
Ki-67 – cell proliferation marker
MIB-1 – clone of anti-Ki-67 antibody.

Craniopharyngiomas (CP) are benign epithelial tumors arising from the remnants of epithelial tissue in the improperly formed pituitary gland or the remnants of the craniopharyngeal duct [30]. CP can be formed in any segment of the craniopharyngeal duct: from the sella turcica to the hypothalamus, and can also occur in the adjacent regions from the nasopharynx to the ventricular system [5, 10, 20, 22, 23, 42].

Despite the histologically benign properties, macroscopically radical resection of CP is associated with a high risk of relapse, reaching from 30% (during the 10-year postoperative period [12]) to 59% (during the 5-year postoperative period [60]). Surgical resection is still considered to be the main method for managing CP. According to different data [7, 36, 52, 61, 62, 69], the probability of radical resection is 50–80%. The current data regarding the efficiency of postoperative radiation are rather ambiguous: from attaining 95% recurrence-free survival [59] to the total inefficiency [60]. CP account for 2–5 and 5.6–13% of all intracranial tumors in adults and children, respectively [46, 53]. The peak incidence of CP is observed in two age groups: 5–14-year-old and 50–74-year-old patients [6].

CP Structure and Mechanisms of Formation

1. Hypotheses of CP formation

The mechanisms of CP formation remain unelucidated. The only fact is known for sure: these tumors are congenital and are most likely to be nonheritable. The reasons for growth initiation in different age groups are unclear. A number of possible and interrelated processes are currently being discussed:

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— cell proliferation caused by disorders of apoptosis (programmed cell death) — activation of anti-apoptotic mechanisms and/or disturbance in sensitivity to growth factors;
— development of cell anaplasia;
— tumor cells acquire properties causing local invasive growth;
— neangiogenesis — formation of blood vessel neoplasms in tumors, resulting in tumor growth.

There are two main acknowledged theories of CP formation: the theory of embryogenesis and the metaplastic one. The former theory proposes that the remnants of pharyngeal epithelium and/or the Rathke's pouch undergo tumor transformation during the development of the anterior pituitary gland. This mechanism presumably bolsters the formation of adamantinomatous craniopharyngiomas (ACP) that most frequently occur among children. The latter theory suggests that metaplasia of the remnants of stratified squamous epithelium develops, giving rise to papillary craniopharyngiomas (PCP) in adults [6, 34, 39, 66].

2. Morphological characteristics of CP

Only 10% of CP have a completely solid structure. The remaining 90% of tumors are characterized by the formation of cysts with different volume. In 60% of CP, the cystic component predominates with respect to its volume [2].

The histological structure of CP is represented by two variants: adamantinomatous and papillary CP, which differ considerably in terms of their biological and clinical behavior.

ACP predominantly occur among children, young people and, less frequently, in elderly people. The histological presentation includes growth of epithelial cells that form bundles of trabecules and round aggregates. The appearance of epithelium differs depending on its localization: the basal layer adjacent to the connective tissue is formed by a single layer of oval cells; the further epithelial cells are less ordered. As they approach the center of the aggregate, the epithelial cells acquire syncytial structure (stellate shape of the cells) and form reticular structures resembling the enamel organ. This CP variant is frequently associated with the development of ceratoid degeneration, formation of horny lamellae and giant-cell granulomas of foreign bodies. The calcification and ossification phenomena are quite typical [24].

Unlike ACP, PCP occur in adults, have a more compact solid structure, and are less likely to contain cysts and petrificates. PCP are formed by well-differentiated epithelium. The layers of stratified non-keratinized squamous epithelium are separated by a loose connective tissue stroma containing a large number of vessels. The mutual arrangement of the stroma and epithelial layers forms papillary structures that are morphologically similar to squamous cell papilloma [14, 31]. PCP containing goblet and ciliated cells are also known as ciliated CP. According to K. Sato [54], they are formed from the basal cells of Rathke’s pouch cysts via squamous metaplasia. According to the WHO classification, CP are grade 1 benign tumors.

2.1. Local invasive growth of CP

Despite their benign nature, CP are prone to infiltrative growth. This occurs due to focal invasion of individual epithelial aggregates to the adjacent brain tissue. These aggregates of tumor cells result in reactive changes in the glial tissue accompanied by the formation of the so-called glial pseudocapsule of CP, which can sometimes be misinterpreted as pilocytic astrocytoma.

The electron microscopic studies of the wall fragments of the third ventricle that had been resected along with CP demonstrated that the apical regions of ependymocytes form folds and lose the “cilia”; however, they acquire a number of multioriented microvilli. The surface cells flattened and sparse; they have a polygonal shape with 3–7 protruding facets. An ultrastructural analysis reveals the existence of various types of several layers of ependymal and subependymal epithelium. Both types of epithelium contain numerous neurofilaments and well-pronounced intercellular contacts. In addition, the foci of cellular disorganization have also been detected [48, 49].

2.2. Epidermal growth factor receptor (EGFR)

EGFR plays an important role in tumor cell migration and infiltration of the medullary substance of ACP. Neither mutations nor amplifications of the EGFR gene have been detected by genetic study of ACP. Nevertheless, activated (phosphorylated) EGFR was detected in tumor fragments infiltrating the medullary substance and localized together with beta-catenin and fascin. Activated EGFR induces tumor cell migration [17].

2.3. Malignization of CP

Malignization of CP occurs rather rarely, in most cases after multiple relapses and radiation. Less than 10 cases of malignant transformation of CP have been reported.

In 2010, M. Ishida [19] reported malignant transformation of CP in a patient who underwent two surgeries and a course of radiation therapy. The bioplates obtained during the first and second surgery were characterized by the typical morphological presentation of ACP. Large foci of basaloid cells with large oval nuclei containing a clearly define nucleolus and frequent mitotic figures the tumor (21/10 of the field) were obtained during the third surgery. The p53 expression was higher as opposed to that in the “benign” regions of the tumor. The fact of tumor malignization was ascertained according to this presentation.

In other studies where malignization of CP was reported, all patients underwent radiation therapy, and high p53 expression in tumor cells was observed in all the cases.
3. Proliferation and neoangiogenesis as factors of CP progression

3.1. Ki-67 antigens (antibodies, clone MIB-1)

Ki-67 protein is a marker of cell proliferation. MIB-1 monoclonal antibodies are used to detect Ki-67 antigen [55]. The labeling index for proliferation markers is low in most CP [65].

The Ki-67 labeling indices (MIB-1 clone) in epithelial cells were found to be higher than those in the tumor stroma; the expression is predominantly detected in pali-sade cells of the epithelial component along the peripheral regions of the epithelial complex.

The MIB-1 labeling index is not an independent criterion of the relapse risk. It lies within the range of 0.1–34.6% (mean value 8.9%; SD 9.8) in adults. In children, it remains within the range of 1.8–15.0% (mean 6.3%; SD 3.7). The MIB-1 labeling index is not considered to be an independent criterion of the relapse risk; however, an increase in this index was observed in children with recurrent CP for each subsequent episode of tumor emergence. The Ki-67 labeling index is used to assess the tumor nature and aggressiveness [44]. According to the other data, the MIB-1 level can vary from 0.4 to 32.5% (mean 10.84%). The MIB-1 level turned out to be 3.4±2.3% in patients with non-recurrent CP. The MIB-1 labeling index for the recurrent tumors was considerably higher (13.2±7.7%).

The “threshold” level of the MIB-1 labeling index (7%) was statistically determined in some studies; above this level, the risk of tumor recurrence significantly increases [37].

The MIB-1 level in adult CP is higher than that among children. The epithelial cells of CP adjacent to the stromal cysts are more active as compared to those being adjacent to the neural tissue. The accumulation of MIB-1 in nuclei differs for the two types of CP [12].

According to some data, the MIB (Ki-67) level is identical for ACP and PCP [12]. However, other data reported that the Ki-67 labeling index and the microvascular density index were stronger pronounced in ACP as compared to those in PCP (22±6 vs. 17±3, \( p=0.05 \); 21±3 vs. 17±3, \( p=0.037 \)); these indices were associated neither to the recurrence nor to the continued growth [60].

3.2. The p53 protein and p53-related proteins p73 and p63

The p53 protein participates in DNA repair processes and in regulation of transcription of the genes regulating apoptosis. An increase in the p53 level in response to DNA damage typically induces apoptosis [32].

When studying the p53 level, expression of its mutant form (i.e., the form that cannot regulate apoptosis) is detected in both ACP and PTP [35].

The presence of concentric foci of epithelial cells in the tumor (\( p=0.04 \)) and high level of p53 expression (\( p=0.022 \)) reliably correlate with the risk of continued growth and probability of relapse [60].

The p63 and p73 proteins are considered to be onco-suppressors. High level of p63 expression is detected in all cellular layers; while p73 expression (from moderate to high) is detected only in the basal cellular layers [35].

The p63 protein participates in regulation of adhesion and viability of epithelial cells [9].

The increased level of p63 expression is detected in most ACP and PCP, which is accompanied by an increased level of the deltaNp63 mRNA isoform [8]. The deltaNp63 isoform is expressed in squamous-cell carcinoma and presumably plays a role in enhancement of aggressiveness in biological behavior of CP cells [35].

In the study conducted by Zh.B. Semenova (Burdenko Neurosurgical Institute) in 2000, no expression of p53, carcinoembryonic antigen, and epithelial membrane antigen has been detected in any of 62 observations. Tenascin expression was detected in the basal membranes and fibroblast cytoplasm. High expression of cer B-b2 oncoprotein was revealed only in ACP (30–100% of cells were stained). Direct correlation between the expression of cerB-b2 and Ki-67 has been established. Furthermore, the Ki-S1 labeling indices were studied (the level varied from 0.3 to 12%). The highest indices were detected for the recurrent tumors. The average level of the labeling index for the proliferating cell nuclear antigen (which was mostly detected in ACP) was 25% and varied from 12 to 45%. The distribution of stained nuclei in all the cellular layers was absolutely homogeneous [1].

3.3. Microvascular density (MVD)

Vascular malformation in the tumor due to proliferation and migration of endothelial cells are one of the key possible mechanisms that explain the aggressive behavior of CP.

The MVD of the tumor can be assessed immunohistochemically using anti-endothelial marker CD34 monoclonal antibodies. The CD105 antigen is reported to be a more specific endothelial marker than CD34 [11].
The MVD level assessed using CD105 turns out to be considerably lower than that determined using CD34 [11]. It is noteworthy that only 2.5% of vessels stained considerably lower than that determined using CD34. The MVD level assessed using CD105 turns out to be lower – integrin alpha-V beta-3 (α vβ3) [65]. Vitronectin participates in regulation (suppression) of proteolysis, which is initiated by plasminogen activator (whose high level determines activity of angiogenesis processes and the tumor growth rate). The low level of integrin alpha-V beta-3 correlates with active angiogenesis and high tumor growth rate [16, 38, 68]. A positive correlation between the MVD value and the Ki-67 labeling index (clone MIB-1) was detected [65].

Pathohistochemical studies reveal a relatively small number of capillaries in the tumor stroma, as opposed to its epithelial component. The immunohistochemical test reveals the expression of vascular endothelial growth factor (VEGF) in epithelial cells of both CP variants ( adamantinomatous and papillary CP). The in situ hybridization (ISH) method detects expression of mRNA of VEGF receptor-2 (VEGFR-2) both in the endothelial component of the tumor and in capillary endothelium.

VEGFR-2 is the key modulator of VEGF activity in endothelial and stromal cells as it plays a significant role in aggressive behavior of CP [64]. Some alternative opinions have also been put forward. According to them, the levels of VEGF and endostatin expression in the epithelial component, as well as the expression levels of other stimulators and inhibitors of angiogenesis are independent of the intensity of MVD [11].

4. Craniopharyngeal cysts and interferon

An assumption has been made that cyst formation in the CP tissue is associated with the level of VEGF expression. VEGF expression in CP with predominantly cystic structure is considerably higher than that in tumors with predominantly solid structure or the ones containing few small cysts, where there may be no VEGF expression at all [63].

A lot of aspects of the mechanism of formation of cystic fluid in CP still remain unclear. Two theories are predominantly discussed: (1) cystic fluid is formed as a result of permeability of the hematonecphalic barrier; (2) it is secreted by the capsule.

Alpha-defensin 1–3 proteins is a crucial component of the cystic contents; its presence may indicate that the immune system participates in cyst formation.

Human alpha-defensin 1–3 accounts for 30–50% of all the proteins in azurophilic granules of neutrophil segmentonuclear leukocytes, which are cells with the known and high antibacterial and antiviral activity. The level of alpha-defensin expression is significantly increased in saliva of patients with squamous-cell carcinoma of the oral cavity, in contents of jaw cysts, and in the plasma of patients with sepsis and meningiomas. Furthermore, the expression level of these proteins decreases after alpha-defensin is injected to the cyst, which correlates with the further clinical outcome.

The possible mechanism of action of interferon participating in this effect has not been elucidated yet: it may exert either a direct effect on squamous epithelial cells of the cysts or an immunomodulating effect due to initiation of the immune system [40, 45].

Antimicrobial protein alpha-defensin 1–3, which is responsible for initiation of the immune response had been detected in cystic fluid of CP before the therapy was started. The protein level considerably decreases in patients who receive conservative treatment. The clinical treatment outcomes correlate with gradual reduction in the level of alpha-defensin 1–3. Detection of alpha-defensin 1–3 eliminates the disturbance of the hematonecphalic barrier from being regarded as a possible reason of formation of cystic fluid and verifies the fact that the immune response participates in cyst formation. The antitumor effect of interferon still needs to be refined [41].

Carboanhydrase IX (CA IX) is an enzyme associated with the tumor and induced by hypoxia; this enzyme cannot be associated with the formation of cystic fluid. In healthy patients, CA IX is not detected in brain tissues; its expression is inhibited by p53 protein.

M. Proescholdt et al. [43] have studied 20 CP samples and found a significant level of CA IX in 85% of cystic CP; the expression intensity correlated with the cyst size. No p53 mutations were detected in the CP studied. The authors additionally studied expression of HIF-1alpha (the hypoxia-inducible factor, which is a transcription factor that responds to the changes in oxygen level in the cellular environment resulting in hypoxia) and found no correlation with the cyst size. According to their data, HIF-1alpha most frequently is not detected in tissues where a high level of VEGF expression was observed.

Authors [43] have ascertained that the regulation mechanism of CA IX has not been thoroughly elucidated; however, neither hypoxia nor p53 plays a significant role in it. They believe that the inhibition of CA IX may turn out to be a potential “target” for the adjuvant targeted therapy of cystic PC.

5. Molecular and genetic features of PC

Mutant D32Y, G34R, and G34V genes, which occur in some skin neoplasms were detected in epithelial cells of CP [25].

CP are monoclonal tumors that are formed after activation of oncogenes localized in certain chromosomal loci. Most tumors are characterized by increased DNA copy number. Reduced copy number is detected much less frequently [47]. Polysomia or chromosomal loss are not typical of primary tumors in the pediatric population. M. Yoshimoto et al. [67] believe that this fact indicates that chromosomal dysbalance does not play a crucial role in the formation of these tumors in children.
Studies of the nuclei of epithelial cells of ACP, which accumulate beta-catenin, have shown an increased expression level of the Axin-2 and BMP4 (bone morphogenetic protein 4) genes. The increased BMP4 expression level supports the theory that ACP is formed from the oral ectoderm. Furthermore, exon 3 mutations were detected in cells accumulating (ACP) and not accumulating (PCP) beta-catenin. No disruptions in the genes responsible for the membrane bonds and active/passive nuclear transport (exons 4, 8—13) have been revealed [18].

5.1. Beta-catenin and WNT signaling pathway

The WNT signaling pathway [50] is a complex cascade of a large number of proteins participating in embryogenesis, tissue differentiation, and carcinogenesis [29]. The disturbance of the WNT signaling pathway is one of the molecular mechanisms of neoplastic cell transformation that is typical of ACP and presumably causes the infiltration of the adjacent brain tissue [18].

Membrane receptors associated with WNT normally initiate the intracellular signaling cascade, resulting in inactivation of the cytoplasmic protein kinase 3beta (GSK3beta) complex. This proteosomic complex participates in degradation of beta-catenin. The inactivation of the complex causes transfer of beta-catenin molecules to cell nuclei, where they interact with the TCF family of transcriptional factors (T-cell factor/lymphoid enhancer factor). The resulting intracellular accumulation of beta-catenin enhances the expression of target genes, such as c-myc and Cyclin D1 and plays the key role in proliferation and formation of cell structure and polarity. In other words, accumulation of beta-catenin in cellular cytoplasm or nuclei stimulates proliferation of tumor cells and inhibits apoptosis. GSK3beta mutations have recently been detected in ACP. Furthermore, this mutation causes the disturbance of the Axin2 gene expression in CP. An increased Axin expression level is the manifestation of the negative association with beta-catenin activity. Increased Axin activity causes degradation of beta-catenin and reduction in its cellular concentration [40]. The WNT—beta-catenin—TCF complex is believed to play a crucial role in the formation of PC [15].

Beta-catenin is accumulated in ACP in nuclei or the cytoplasm of the cohesive cells localized in the concentric foci and in cells that can be transformed to the ghost cells (that never express Ki-67). The cohesive cells in the concentric foci do not express cytokeratins. Hyperexpression of beta-catenin in cellular nuclei of typical ACP correlates with heterozygous mutations of the beta-catenin gene. Nuclear expression of beta-catenin is not observed in ACP with irregular structure and PCP with the well-defined squamous component. These tumors show no mutations in the beta-catenin gene. These data attest to the morphogenetic heterogeneity of CP. The pathogenesis of typical ACP is associated with the disturbance of the WNT-signaling system, transducing a greater signal to the morphogenesis of concentric foci and ghost cells as compared to the other proliferative stimuli [24].

Furthermore, beta-catenin expression in some cases was detected in palisade cells, where Ki-67 was typically detected [8].

ACP and PCP differ clinically, morphologically, and genetically as well. The mutant beta-catenin gene was detected only in ACP. In all the cases, beta-catenin was accumulated both in the cytoplasm and cellular nuclei of these tumors. PCP are characterized by the membrane expression of beta-catenin only. In addition, the mutant beta-catenin gene was detected both in the epithelial and mesenchymal cells of ACP, which attests the biphasic nature of these tumors [57].

5.2. Odontogenic proteins

ACP are characterized by histological similarity with some odontogenic tumors (ameloblastoma, calcifying odontogenic cyst), although no data have been obtained supporting the fact that ACP develops from odontogenic epithelium [58].

The LEF1 protein factor, which gives rise to tooth enamel, is expressed only in tooth and plays a significant role in tooth development along with beta-catenin. The emergence of this factor and other odontogenic proteins is indicative of odontogenic differentiation of epithelium.

ACP are characterized by odontogenic epithelial differentiation. Different levels of expression of enamel proteins (including amelogenin, enamelin and enamelysin) were revealed in all ACP, predominantly in the ghost cells. LEF1 was also heterogeneously expressed in ACP, in a manner similar to the accumulation of beta-catenin in cell nuclei. Expression of enamel proteins and LEF1 has been detected in none of PCP.

A hypothesis has been made that it is accumulation of beta-catenin that activates transcription of the beta-catenin/LEF1 complex, which may play a crucial role in tumor formation [58].

5.3. Oncogenesis markers

5.3.1. Cytokeratins

Cytokeratins (CK) are the proteins forming intracellular intermediate filaments of the epithelial cell cytoskeleton of [56]. Controversial data were obtained by assessing the expression levels of CK in CP. Some researchers have found that CK8 is detected in most CP, while CK20 is predominantly revealed in the Rathke’s pouch cysts [27].

The other authors [66] report that, unlike the cysts in the Rathke’s pouch and the intermediate lobe of hypophysis, CP do not express CK5 and CK20. When studying the recurrent CP, CK8/CK18/CK19 expression was detected in 64% of tumors; expression of CK5, laminin 8, and carcinoembryonic antigen was detected...
in 42, 62, and 21% of tumors, respectively. No significant difference between the expression levels of CK, laminin, carcinoembryonic antigen, and gliofibrillar acid protein (GFAP) was detected in ACP and PCP [60].

5.3.2. Cathepsins

Intracellular proteases (cathepsins) are believed to actively participate in oncogenesis. More than 15 cathepsins are known today. Cathepsin B is a cysteine protease [3]. Cathepsin B expression increases when the primary brain tumors are malignized; however, its level shows no correlation with the aggressiveness of CP [33]. Being an aspartic protease, cathepsin D is associated with tumor invasiveness [13]. According to other reports [33], it is detected in prostate cancer cells, where it participates in production of angiostatin, the potential angiogenesis inhibitor that decreases the growth of the primary tumor and angiogenesis-dependent metastases. The increase in cathepsin D level in CP cells (that are typically better differentiated) increases the angiostatin level, reduces the risk of relapse, and slows down the growth rate of CP.

Cathepsin K is a cysteine protease belonging to the papain class. It is capable of degrading osteoproteins: type I collagen, osteopontin and osteonectin, thus causing osteoporosis. The increased cathepsin K level was detected in recurrent CP characterized by reduced cell differentiation [33].

The expression intensity of cathepsins D and B show a good correlation with the expression level of retinoic acid receptor (RAR)-beta, while the expression level of cathepsin K correlates with that of RAR-gamma. The recurrent CP are characterized by an increased cathepsin D level and reduced cathepsin K level [33].

5.3.3. Macrophage migration inhibitory factor

The macrophage migration inhibitory factor (MIF) is presumably another factor of CP oncogenesis. MIF mRNA (matrix ribonucleic acid) is normally expressed in skin and nerve cells; the effect of MIF has been described for various skin pathologies and varied from inflammation to hyperplasia. MIF is believed to stimulate tumor growth and angiogenesis, since anti-MIF antibodies efficiently terminate the aforementioned processes. MIF expression correlates with the risk of recurrent CP [40]. According to other data [28], the MIF level in cells of CP with rapid recurrence was found to be considerably lower than that in cells of tumors with slow recurrence.

5.3.4. Galectin

A decreased galectin-3 level is also observed in CP with rapid recurrence. The antiapoptotic role of galectin-3 is determined by its participation in phagocytosis, while the reduction in its level disturbs the usual biological elimination of the remnant embryonic tissues [28, 40].

6. Sex hormone receptors in CP cells

6.1. Estrogen and progesteron receptors

An increased level of mRNA expression for estrogen and progesterone receptors is revealed in proliferating epithelial CP cells. These receptors can be markers of the potentially high tissue differentiation, since their co-expression is associated with a low risk of tumor recurrence [21].

6.2. Retinoic acid receptors and cathepsins

Retinoic acid receptors (RAR) are a group of nuclear steroid and thyroid hormone receptors. Several isoforms of these receptors are known: alpha, beta, and gamma. There is a clear dependence between anaplasia with the risk of CP recurrence and RAR expression. RAR are one of the biological regulators of maturation of various endothelial types, including epidermal tissue. Correspondingly, the level of various RAR isotypes differs depending on the level of maturation and differentiation of epidermal cells. A reduced level of RAR-beta and increased level of RAR-gamma isotypes have been detected in recurrent ACP [33].

Conclusions

It should be mentioned that a significant advances in studying CP morphology have been achieved over the past decade. The number of various factors associated with the development of CP, which can be assessed using different methods, approaches 40 (see Table).

The available data illustrate that ACP and PCP are morphologically different tumors, which requires one to use the differentiated approach in further research.

After we have compared different studies used to prepare this review, we can claim that none of these studies was comprehensive. The largest number of observations was no greater than 60. ACP was the most frequently studied type of CP. The number of markers analyzed in a single study was no greater than 6–8.

It is obvious that the next stage, in addition to revealing new oncogenetic factors, should consist in analyzing the relationships between the data that have already been obtained in various studies and the clinical outcomes of different treatment options of CP. The aim of this analysis is to determine the most significant prognostic criteria of the risk of rapid progression and emergence of recurrent craniopharyngiomas. The Burdenko Neurosurgical Institute is a specialized neurosurgical hospital where some 100 patients with craniopharyngiomas, both adults and children, are annually operated. Such a topical clinical and morphological study can be carried out using the facilities of this institution.

Another important current task is to determine other possible “points of action” of targeted drugs in the oncogenesis of CP. Thus, it has been demonstrated that Gefitinib (an antitumor drug belonging to the anilino-
quinoxaline class, which selectively inhibits tyrosine kinase of the epidermal growth factor) reduces the mobility of tumor cells and fascin expression and activates apoptosis. Affecting the EGFR signaling pathway by targeting drugs (such as gefitinib) can be used for drug therapy in patients with CP [17].

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Craniopharyngiomas are tumors of complex structure and histogenesis. Their histological behavior is often unpredictable. From the conventional morphological perspective, craniopharyngiomas exhibit no strongly noticeable signs of neither benign nor malignant potential.

Modern morphology significantly relies on molecular biology and uses this discipline for its development. Nowadays, there are multiple facilities for studying the oncological, morphogenetic, and etiopathological aspects of craniopharyngeal development and behavior at a new level.

The authors of this review have summarized a large body of recent specialized literature on morphology and molecular biology of craniopharyngiomas. An attempt to summarize and systematize the most significant biomarkers among the ones that have been studies was made with allowance for the potential practical significance for diagnosing, prognosing the treatment outcomes, and planning combined therapy. The review focuses on the most significant aspects of the emergence, development, progression, and malignization of craniopharyngiomas.

Attention has also been paid to the current advance and knowledge in the development and histogenesis of two major craniopharyngioma types — adamantinomatous and papillary craniopharyngiomas, which have specific features and are considered to be completely different diseases by some authors (this point of view is reasonable, although disputable as well).

The absence of comprehensive original studies devoted to craniopharyngiomas in Russian literature over the past 10 year could hardly leave the character of this review unaffected. The authors grope for those data and those published results that can be extremely useful for their further research (as well as research conducted by other scientists) devoted to the comprehensive, multi-level, and multi-factor studying of craniopharyngiomas, the mysterious and insufficiently studied group of tumors.

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Brain Tumors: Analysis of Epidemiological Figures and the Status of the Neuro-oncology Service in the Ulyanovsk Region

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The incidence of brain tumors was studied, including the analysis of epidemiological figures and the status of the neuro-oncology service in the Ulyanovsk region during 1996–2005. This article demonstrates a lack of early brain tumor diagnosis in the region owing to insufficient equipment of medical care facilities and the low level of expertise among primary care physicians. The risk factors for the development of complications and increased postoperative mortality are defined. The uniform algorithm of medical care for brain tumor patients will allow one to considerably improve the treatment outcomes.

Keywords: epidemiology, brain tumors, risk factors.

One of the most topical problems of modern neurosurgery is associated with brain tumors (BT) because of an increase in incidence of neuro-oncological diseases, high mortality and degree of invalidization among patients, and significance of the social and economic aspects related to it [1, 4–6].

The annual incidence of BT varies from 7.42 to 13.9 per 100,000 population. According to the data obtained in different epidemiological studies [2–5, 7], it tends to increase.

A clear trend toward the increase in mortality associated with neuro-oncological diseases has been observed over the past 50 years [1, 4, 5].

In order to analyze the activity of oncological institutions, to assess the level, and to further plan the oncological care, one needs to compare the status and the reasons for the increased incidence and mortality with the figures related to the activity of the oncological service. These data are both of significant fundamental and practical interest, since they are essential for current and long-term planning of the activity of the oncological service in Russian provinces [1, 3, 5].

This work was aimed at studying the incidence of brain tumors in the Ulyanovsk region and determining the reasons for late diagnosis and the methods to improve the treatment outcomes.

Material and Methods

A retrospective analysis of 545 medical records of brain tumor patients who received inpatient treatment at the Department of Neurosurgery of the Ulyanovsk Regional Clinical Hospital № 1 and at the Specialized Pediatric Center of Neurosurgery over the period from 1996 to 2005 was carried out. An analysis of 16,780 postmortem examination protocols was also conducted.

Two computed tomography scanners and an MRI scanner operated in the Ulyanovsk region during the period under study. Only cerebral angiography could be performed at the Department of Endovascular Surgery. The neurosurgical operating rooms were not equipped with microscopes. The WHO classification of the tumors of the central nervous system was used for studying the histological types (P. Kleihues, W. Cavenee, 2000).

The functional status of adult and adolescent patients was evaluated according to the Karnofsky scale; that of children was evaluated using the Lansky scale. The Karnofsky score < 60 was considered to be an indicator of invalidization.

According to their localization, supratentorial tumors were classified into hemispheric, median, and optic chiasm cell tumors. The subtentorial tumors were subdivided into hemispheric, median, cerebellopontine angle, and brain stem tumors.

All the tumors in patients in the analyzed group were subdivided into three groups: less than 3 cm, 3–6 cm, and over 6 cm.

Results and Discussion

A total of 870 residents of the Ulyanovsk region with brain tumors have been detected within the period of 1996–2005: 767 adults, 20 adolescents, and 83 children. Among them, 545 patients underwent inpatient examination and treatment.

The analysis of 16,780 postmortem examination protocols has revealed 325 brain tumors that had not been
diagnosed *intra vitam*: 323 tumors in adults and 2 tumors in children.

The group of examined patients consisted of 263 (48.3±2.1%) males and 282 (51.7±2.1%) females (*p* > 0.05). The number of adults, adolescents, and children among the patients was 444 (81.5±1.7%), 20 (3.7±0.8%), and 81 (14.8±1.5%), respectively. The male : female ratio was 1:1.07.

The number of males and females among adult patients was 213 (48±2.4%) and 231 (52±2.4%), respectively; insignificant (*p* > 0.05) predominance of males (11(55±11%)) over females (9(45±11%)) was observed for the adolescent group.

Among pediatric patients, the number of boys and girls was 39 (48.1±5.5%) and 42 (51.9±5.5%), respectively; *p* > 0.05. The maximum number of BT patients was detected among the age group of 12–14-year-old patients; insignificant (*p* > 0.05) predominance of boys was observed. The group of children aged 8–11 years ranked second: 24 (29.6±5.1%) patients.

The average annual incidence rate of BT (with allowance for the biopsy data) in the Ulyanovsk region during the period from 1996 to 2005 was 6 cases per 100,000 population: 6.9 cases among adults; 2.8 cases among adolescents; and 3.3 cases among children. The maximum incidence rate was observed in 2005 (8.1 cases per 100,000 population); the minimum incidence rate was observed in 1999 (5.1 cases per 100,000 population).

The average annual BT mortality rate in the Ulyanovsk region during the period from 1996 to 2005 was 2.2 deaths per 100,000 population (2.8 and 0.4 deaths among adults and children, respectively). 325 BT cases that had not been diagnosed *intra vitam* were identified by autopsy: 323 cases (99.4±0.4%) in adult and 2 cases (0.6±0.4%) in children patients. Among the BT detected on a cross-section, the disease progression was asymptomatic in 124 (38.1±2.7%) cases (all detected among patients) and was not the reason for death. In the remaining cases, 201 (61.8±2.7%) of BT detected by autopsy were the cause of death of the patients but had not been diagnosed *intra vitam*. The diagnosis of brain tumor was *intra vitam* verified only in 116 (26.3±2.1%) patients: 108 (93.1±2.4%) adults and 8 (6.9±2.4%) children. An increase in neuro-oncological mortality was observed during the period under study: from 1.9 in 1996 to 2.9 in 2005 per 100,000 population.

In the group of examined patients, the number of supratentorial and subtentorial BT was 76.7±1.8 and 23.3±1.8%, respectively. In the group of adults, the ratio between the supratentorial and subtentorial BT was 4:1, while being 1:3.1 in the group of children. As can be seen, the predominance of supratentorial tumors in adult patients is considerably less stronger pronounced in children.

We analyzed the onset of the disease and determined that the period between the first complaints and diagnosis was shorter than 1 year in 377 (69.2±2%) patients. In 116 (21.3±1.7%) patients, this period was shorter than 1 month.

When evaluating the functional status, it has been ascertained that 47±2.1% of BT patients were admitted to hospital during the decompensation stage (score 50 and lower).

At the moment of admission to hospital, the number of patients with tumor size below 3 cm was 84 (15.4±1.5%); 3–6 cm, 373 (68.4±2%); and over 6 cm – 88 (16.2±1.6%). Brain tumors with size 3 cm and over were observed in 85% of adult patients and 81% of children with BT.

A total of 529 patients were subjected to surgical treatment. In the group of adult and adolescent patients, all the patients (100%) underwent surgical treatment. In the group consisting of 81 children with BT, surgical interventions were performed only in 65 patients (80.2±4.4%). Sixteen BT (19.8±4.4%) with third ventricle, pineal nuclei, and tumors infiltrating the brainstem were given referrals to the central Russian hospitals.

The amount of surgical intervention was as follows: total tumor resection was performed in 293 (55.4±2.2%) patients; subtotal tumor resection was carried out in 169 (31.9±2%) patients; and partial resection, in 28 (5.3±1%). Cerebrospinal fluid shunt surgeries (CFSS) were performed in 8 (1.5±0.5%) patients. Complete tumor resection combined with CFSS was carried out in 22 (4.2±0.9%) patients; subtotal resection of tumor combined with SFSS was carried out in 8 (1.5±0.5%) patients; 1 (0.2±0.2%) patient was subjected to partial tumor resection and CFSS.

The histological conclusion could be made in 478 (87.7±1.4%) patients. According to the histological classification, the neoplasms were subdivided into the following groups: tumors of neuroepithelial tissue – in 203 (42.5±2.3%), peripheral nerve tumors – in 15 (3.1±0.8%), meningeal tumors – in 181 (37.9±2.2%), lymphoid and hematopoietic tissue tumors – in 1 (0.2±0.2%), germ cell tumors – in 7 (1.5±0.5%), tumors of the “Turkish saddle” region – in 41 (8.6±1.3%), and metastatic tumors – in 30 (5.5±1%).

Among men, astrocytoma (17.6±1.7% of all histologically verified tumors) was the predominant tumor type in the group of intracerebral tumors, while meningeal tumors (14.4±0.6%) were the most common type belonging to the group of extracerebral tumors. In females, these figures were 11.9±1.5 and 23.4±1.9%, respectively.

146 cases (27.6% of all the patients operated on) of postoperative complications have been observed, including bronchopulmonary complications – 70 (13.2±1.5%), secondary brain ischemia – 24 (4.5±0.9%), hemorrhage...
in the tumor bed – 21 (4±0.9%), meningitis and meningoencephalitis – 14 (2.7±0.7%), liquorrea – 9 (1.7±0.6%), acute cardiac insufficiency – 6 (1.1±0.5%), and pyoinflammatory complications – 2 (0.4±0.3%). The risk factors for the development of postoperative complications included symptoms of decompenstation of the patients’ condition, subtotal territory of the process along the median line and near the cerebellopontine angle, functional status score < 60, tumor size over 6 cm, and incomplete resection of the tumor.

The postoperative mortality rate in our study was 21.9%: 12.3% among children; 24.3% among adults; and 0% among adolescents. The following factors contributed to the increase in postoperative mortality: localization of tumors along the median line and near the cerebellopontine angle, tumor size > 6 cm, incomplete resection of the tumor, symptoms of decompenstation of the condition at admission to hospital, and an increase in patient’s age.

Among 545 patients, 82 (17±1.7%) patients received radiation therapy; 17 (3.6±0.9%) patients received chemotherapy; and 49 (10.3±1.4%) patients received both radiation and chemotherapy.

Thus, adjuvant therapy was used only in 148 patients (31±2.1% of the total number of all histologically verified BT cases).

The study conducted gives grounds to report low detection frequency of brain tumors in the Ulyanovsk region. Almost in half of all cases, BT were revealed by postmortem examination. We believe that the reason for the low detection frequency of BT is the insufficient diagnostic facilities of the care institutions in the region and low level of expertise among primary care physicians. The insufficient equipment of surgical facilities also affects the treatment outcomes.

In order to prevent late diagnosis of BT and to reduce the risk of complications and postoperative mortality, one needs to adhere to the uniform algorithm of medical care for brain tumor patients.

Conclusions

1. The total average annual incidence rate of BT (with allowance for the autopsy data) in the Ulyanovsk region during the period from 1996 to 2005 was 6 per 100,000 population: 6.9 among adults, 2.8 among adolescents, and 3.3 among children. The maximum incidence rate, 8.1 per 100,000 population, was observed in 2005; the minimum incidence rate (5.1) was observed in 1999. Neuroepithelial tumors (42.5±2.3%) statistically insignificantly dominated over the meningeal tumors (37.9±2.2%).

2. The problems of late diagnosis of BT, a significant number of complications, and high postoperative mortality exist in the Ulyanovsk region. Up to 47% of all patients were admitted to hospitals during the phase of clinical decompenstation (Karnofsky score < 50). Over 85% of tumors were > 3 cm in size. The major reason is the lack of computed tomography scanners in the care facilities. The insufficient neuro-oncological alertness among primary care physicians has also an effect on the timely diagnosis.

3. There is no clear continuity system among the physicians rendering care to BT patients. There is no full-fledged system for registration of patients. Only 31% of patients operated on at hospitals of the Ulyanovsk region received adjuvant therapy. In order to prevent late diagnosis and reduce the risk of complications and postoperative mortality, one needs to adhere to the uniform algorithm of medical care for brain tumor patients. It is reasonable to input the data on patients with tumors of all histological types to a uniform registry, allowing one to edit the data at all stages of medical care.

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Commentary

This study provides an objective characterization of the situation in Russian neurosurgery that used to exist in the late XX and early XXI centuries. The data collected by the author has been thoroughly analyzed and presented in a form suitable for meta-analysis. Let us comment on the latter.

The paper characterizes patients with nervous system (NS) tumors, who received care at two neurosurgical hospitals of the Ulyanovsk region during the period between 1996 and 2005. It was implied that all the patients in the region sought medical help at these hospitals (either for treatment or referral to treat-
ment) and have been registered. However, it is clear that a significant number of patients have not been taken into account. The arguments for that are listed below:

1. NS tumors were detected *intra vitam* in 545 patients and *post mortem* in 325 patients. Autopsy was obviously carried out not for all the death cases. Unfortunately, the data for the Ulyanovsk region over the period of 1996 to 2005 are unavailable for us. However, according to the data provided by the Russian Federal State Statistics Service, the population of the region was 1,304,990 in 2009; the number of people who died in 2009 was 20,403 (http://www.gks.ru/dbscripts/munst/munst73/DBInet.cgi). Proceeding from the latter figure (which hardly has substantially changed), a conclusion can be drawn that autopsy (the total number 16,780 during 10 years) was carried out for less than 10% of the death cases. Hence, it is inconsistent to include the NS tumors detected only during a surgery or *post mortem* to the calculation of the incidence rate. If one recalculates the number of NS tumors detected *post mortem* to the number of autopsies, the figure of 19.4 per 100,000 death cases per year will be obtained.

2. Some patients could have sought primary care at hospitals located outside the Ulyanovsk region (and Russia). It is obvious from the text of the study that this flow has not been taken into account to the full extent. 19 children who were referred to receive care at the central hospitals are reported. However, the number of patients from the Ulyanovsk region operated on for NS tumors in 2002–2005 at the Institute of Neurosurgery alone was 64.

3. According to the recent reports of the Central Brain Tumor Registry of the United States, the annual incidence of primary tumors of the central nervous system during the period between 2004 and 2008 in the United States was 20.6 per 100,000 population (http://www.cbtrus.org/2012-NPCR-SEER/Table5_0408.pdf). The authors have reported that the increase in this indicator with years is probably associated with improved diagnosis and registration rather than an increase in the incidence rate. Meningiomas (35%) are the most common type of primary NS tumors.

4. The incidence rate of secondary (metastatic) NS tumors is higher than that of primary tumors. In the data presented by the author, the percentage of secondary tumors was 5%.

Hence, the following conclusion can be drawn: the incidence rate calculated by the author has been significantly underestimated. While the medical statistics is only being developed in Russia, we would recommend one to use the US data when planning to render medical care to neuro-oncological patients: ~ 20 patients with primary NS tumors and over 20 patients with metastatic tumors per 100,000 population per year.

Attention should be paid to some other results of the study, as well. The comparison of the statistical data on autopsies and surgeries demonstrates that NS tumors were detected *intra vitam* in a minority of patients. The main reason for that was associated with the lack of diagnostic equipment: during the period under study, there were only two computed tomography scanners and an MRI scanner in the region with population over 1.3 million people. 47% of patients in the state of decompensation with the Karnofsky score less than 50 were hospitalized. Correspondingly, the postoperative mortality rate was 21.9%. Histological diagnosis was not made in 12% of the operated patients. We have found out from communicating with our colleagues that the situation in the Ulyanovsk region has recently changed: new tomography scanners have been purchased and now operate; the frequency of NS tumor detection has been improved, and the invalidization and mortality indicators have decreased.

These remarks do not reduce the value of the study, while the indication of some drawbacks will allow both the author and other researchers to avoid them in future. We would recommend the author to continue the study with an emphasis on establishing the correlation between the improvement of medical care facilities, detection frequency of CNS tumors, and treatment outcomes. The results of this study will allow one to substantiate the requirements to the equipment of regional neurosurgical facilities not only in the Ulyanovsk region but in other Russian provinces as well.

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