APPLICATION OF THE APPARENT DIFFUSION COEFFICIENT IN PREOPERATIVE ASSESSMENT OF THE PROLIFERATIVE POTENTIAL OF SPINAL TUMORS

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Objective. To analyze and compare the measured values of apparent diffusion coefficient (ADC) in tumors of the spinal canal with cell density and Ki-67 index of proliferative activity.

Material and Methods. The study included diffusion-weighted MR images of 36 patients with different types of tumors of the spinal canal. In the morphological study of tumors, the degree of malignancy according to the WHO classification, the value of the Ki-67 index, and cell density were assessed.

Results. The average ADC of the extradural tumors G = I–II and G = III–IV was 1390.0 ± 94.8 mm^2/s and 821.3 ± 111.1 mm^2/sec, respectively. For intradural extramedullary neoplasms G = I–II, the ADC was 1328.7 ± 172.1 mm^2/sec, for G = III – 957.6 ± 50.7 mm^2/sec. Intramedullary tumors G = I–II had an average ADC value of 1604.6 ± 28.7 mm^2/sec, and tumors G = III – 1066.5 ± 74.2 mm^2/sec. For extradural tumors G = I–II, the Ki-67 index varied from 2 to 4 %, and for tumors G = III–IV – from 12 to 27 %; in the group of intradural extramedullary tumors G = I–II – from 1 to 5 %, for tumors G = III – from 7 to 11 %; for intramedullary tumors G = I–II – from 2 to 6 %, and for G = III tumors – from 7 to 19 %.

Conclusion. The diffusion-weighted MRI with ADC counting can be used as an additional non-invasive method for preoperative evaluation of the proliferative potential of a number of spinal canal tumors.

Key Words: spinal canal tumors, diffusion-weighted MRI, apparent diffusion coefficient, diffusion-weighted image, cell density, Ki-67 index.

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Spinal canal tumors include a large group of heterogeneous space-occupying lesions. This group of tumors is characterized by a high prevalence of malignant forms, mainly due to metastases [2, 3]. Currently, MRI is the gold standard in diagnostics of spinal canal tumors [11]. However, many space-occupying lesions have similar signal characteristics on standard T1- and T2-weighted images (T1WI, T2WI), which significantly complicates the differential diagnosis and the choice of adequate management of patients [8, 14].

Diffusion-weighted MRI is an instrumental technique providing tumor tissue images that are weighted by diffusion of free water molecules at the cellular level. In this case, the degree of water molecule diffusion can be estimated numerically by the apparent diffusion coefficient (ADC). The array of ADC values for a given biological structure is a functional map of diffusion-weighted images (DWIs) [4].

Studies on the use of diffusion-weighted MRI in spinal canal tumors are not numerous and often contradictory. A number of authors have noted [7, 12, 17] that certain histological tumor types are characterized by a correlation among the ADC value, cell density, and proliferative activity index (Ki-67). Other researchers do not see this relationship [6, 19]. Given the histological diversity of spinal canal tumors and a high rate of metastases, it is important to correctly assess the proliferative potential of a space-occupying lesion as early as at the stage of neuroimaging examination in order to plan the scope and type of surgery [1, 5, 18].

The study objective was to analyze and compare the ADC values with the cell density and proliferative activity index Ki-67 in spinal canal tumors as well as to assess the applicability of diffusion-weighted MRI in a complex study of the proliferative potential of these space-occupying lesions.

Material and Methods

The study involved diffusion-weighted MR images of 36 patients with spinal

canal tumors who underwent surgery at the Neurosurgical Center of the Railway Clinical Hospital at the Irkutsk-Passenger Station in the period between 2014 and 2017. There were 19 females and 17 males; the mean age of patients was 52.8 ± 11.4 years.

MR images (T1WI, T2WI, and DWI) were acquired with a Siemens Magnetom Essenza 1.5 T apparatus before and after administration of a contrast agent (Fig. 1a–c). In a T1WI study, the following parameters were used: matrix 384 × 387, repetition time (TR) = 650 ms, echo time (TE) = 9.6 ms, number of excitations (NEX) = 1, slice thickness = 4 mm, and field of view (FOV) = 30 × 30. In a T2WI study, the parameters were as follows: matrix 384 × 288, TR = 4,000 ms, TE = 43 ms, NEX = 1, slice thickness = 4 mm, and FOV = 30 × 30. In a DWI study, the following set of parameters for DW MRI with SE-echoplanar imaging (EPI) was used: matrix 160 × 128, TR = 7,500 ms, TE = 83 ms, NEX = 6, slice thickness = 4 mm, and FOV = 30 × 30. We used b-factor values of 400 and 800 s/mm^2. The scan time was 6 min 30 s, on average. The ADC was calculated using DWI with the largest diameter of a space-occupying lesion, the region of interest did not involve cystic and necrotic tumor areas. The ADC was calculated using the "RadiAnt DICOM Viewer" software.

In all cases, tumors were resected, as radically as possible, using a microneurosurgical techniques and an operating microscope. In a number of cases, resection of spinal canal tumors involved the use of 5-aminolevulinic acid-based fluorescence navigation in the "Blue-400" imaging mode, an ultrasonic surgical aspirator, an intraoperative neuromonitoring system, and a carbon dioxide laser.

All removed space-occupying lesions were examined by an experienced pathomorphologist. In the morphological study of tumors, the following parameters were evaluated: the WHO tumor grade, proliferative activity index Ki-67 (by using monoclonal antibodies MIB-1), and cell density of the tumor tissue (Fig. 1d, e). Cell density was calculated using the "Image J" software, under total microscope magnification of 400 ; the density value was expressed as cells/mm^3.

Data were statistically processed using the "Microsoft Excel 2010" software. All measurements were verified for the normality by means of the Kolmogorov-Smirnov test. The obtained data were evaluated using methods of descriptive statistics (absolute and relative values). Categorical variables are expressed as a percentage. A comparative analysis of ADC values was performed using the Mann-Whitney U-test.The Spearman coefficient was used to evaluate a correlation among ADC values, cell density, and Ki-67 index values in tumors. The significance threshold p was selected to be 0.05. The study was approved by the ethics committee of the Irkutsk State Medical University. All patients included in the study gave written informed consent.

Results

Based on the anatomical principle, spinal canal tumors were represented by the following types: extradural tumors (n = 9), intradural extramedullary tumors (n = 22), and intradural intramedullary tumors (n = 5). Histological tumor variants are shown in Table.

In the group of extradural space-occupying lesions, the mean ADC values for tumors of low-grade (I–II) and high-grade (III–IV) malignancy were 1390.0 ± 4.8 mm^2/s and 821.6 ± 111.1 mm^2, respectively. Comparison of the mean ADC values revealed a significant difference between grade I–II and grade III–IV tumors (p = 0.008, Fig. 2a). In the group of intradural extramedullary neoplasms, grade I–II and grade III tumors had the mean ADC values of 1328.7 ± 172.1 mm^2/s and 957.6 ± 50.7 mm^2/s, respectively. A significant difference was found upon comparison of the mean ADC values among extramedullary tumors of varying degrees of malignancy (p = 0.003, Fig. 2b). The group of grade I–II and grade III intramedullary tumors had the mean ADC values of 1604.6 ± 28.7 mm^2/s and 1066.5 ± 74.2 mm^2/s, respectively. Comparison of the mean ADC values for these tumor groups revealed no significant differences (p = 0.817, Fig. 2c).

The cell density in tumors of different grades of malignancy varied widely: from 895 to 1772 cells/mm^3 (mean, 1144 ± 353cells/mm^3) in the group of extradural neoplasms; from 862 to 1616 cells/mm^3 (mean, 1354 ± 186 cells/mm^3) in the group of intradural extramedullary tumors; from 862 to 1616 cells/mm^3 (mean, 1254 ± 247cells/mm^3) in the group of intradural intramedullary space-occupying lesions. In all groups, there were no significant differences in the cell density between tumors of different grades of malignancy (p = 0.623, p = 0.471, and p = 0.533 for extradural, intradural extramedullary, and intramedullary space-occupying lesions, respectively).

The proliferative activity index in different tumor groups also varied widely. For example, the index amounted to 2 to 4 % (mean, 2.80 ± 0.83 %) and 12 to 27 % (mean, 19.75 ± 6.60 %) for grade I–II and grade III–IV extradural tumors, respectively; 1 to 5 % (mean, 2.90 ± 1.50 %) and 7 to 11 % (mean, 9.00 ± 2.80 %) for grade I–II and grade III intradural extramedullary tumors, respectively; 2 to 6 % (mean, 2.3 ± 0.57 %) and 7 to 19% (mean, 17.4 ± 7.35 %) for grade I–II and grade III intradural intramedullary tumors, respectively. Comparison of the mean Ki-67 values among tumors of varying degrees of malignancy revealed significant differences in groups of extradural and intradural extramedullary space-occupying lesions (p = 0.007; p = 0.002; Fig. 3a, b).

A correlation analysis between ADC values and cell density in different tumor groups showed no statistically significant dependence. Evaluation of a correlation between the ADC and the proliferative activity index Ki-67 revealed a marked inverse correlation in groups of extradural (r = -0.88; p = 0.004) and intradural extramedullary tumors (r = -0.699; p = 0.0057; Fig. 4a–c).

Discussion

To date, there are a number of studies devoted to the use of diffusion-weighted MRI in the differential diagnosis of

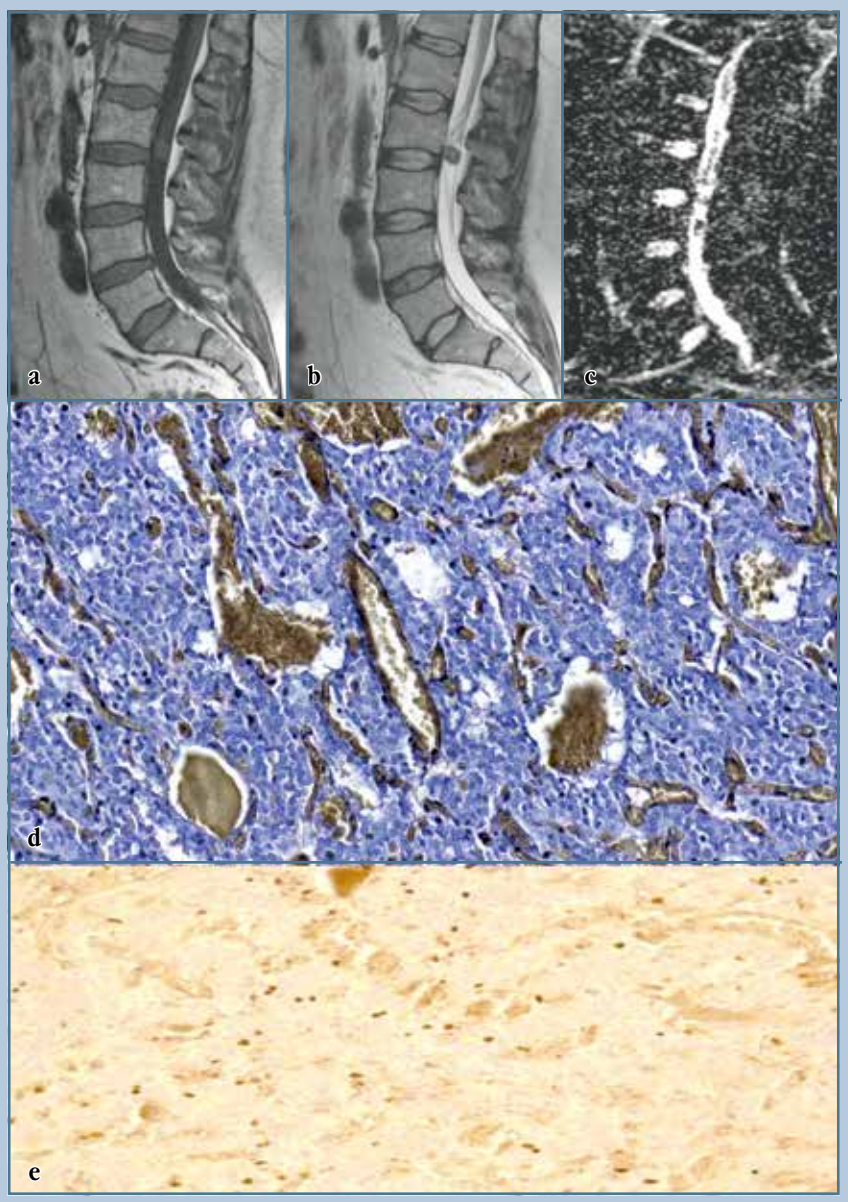

Fig. 1
MRI and a pathomorphological picture of an intradural extramedullary space-occupying lesion at the L2 level: **a** – a T1-weighted image; **b** – a T2-weighted image; **c** – a diffusion-weighted image with an apparent diffusion coefficient of 978 mm^2/s; **d** – light microscopy, hematoxylin-eosin staining, hemangioblastoma (grade I), cell density of 1372 cells/mm^3; **e** – staining with MIB-1 monoclonal antibodies, Ki-67 proliferative activity index = 3 %

various tumors. However, the results of these studies are interpreted ambiguously. For example, Hasan et al. [10] found significant differences in ADC values of intramedullary low- and high-grade gliomas. Hakyemez et al. [9] clearly demonstrated that ADC values of typical brain meningiomas (grade I) were significantly higher than those of atypical and anaplastic meningiomas (grade II and grade III). On the other hand, an analysis of brain meningiomas of varying degrees of malignancy by Sanverdi et al. [15] revealed no significant differences among ADCs. Similar results were obtained in a study by Pavlisa et al. [13].

An analysis of the world literature revealed single reports on the correlation between ADC and Ki-67 values for different tumors. A study by Karaman et al. [12] demonstrated a strong inverse correlation between ADC and Ki-67 values for non-small cell lung cancer. Wang et al. [17] obtained similar results for endocrine tumors of the pancreas. On the other hand, Wu et al. [19] found no correlation between ADC and Ki-67 values for diffuse large B-cell and follicular lymphomas. Contradictory results were also obtained for central nervous system tumors, in particular meningiomas. Tang et al. [16] noted a statistically significant correlation between ADC and Ki-67 values for both grade I meningiomas and grade II and grade III meningiomas. Ginat et al. [7] reported no significant correlation between ADC and Ki-67 values for grade III meningiomas. Fatima et al. [6] also found no significant correlation between ADC and Ki-67 values. In our opinion, this ambiguity of the findings may be explained by different approaches authors calculate the ADC using the DWI data.

Our findings are largely consistent with the world literature data. The mean ADC values of low-grade tumors are significantly higher than those of high-grade tumors, in particular in groups of extradural and intradural extramedullary space-occupying lesions. Furthermore, these groups of spinal canal tumors are characterized by a statistically significant correlation between values of the ADC and the proliferative activity index Ki-67. The obtained data suggest that the ADC indirectly reflects pathomorphological changes in tumor tissue.

The main purpose of this study is to use the ADC in preoperative assessment of the proliferative potential of spinal canal tumors. Our findings suggest that extradural and intradural extramedullary tumors have a high proliferative potential at ADC values of less than 900 mm^2/s

Table
Histological variants of spinal tumors

Tumor	WHO tumor grade			
	Grade I	Grade II	Grade III	Grade IV
Extradural (n = 9)	Cavernous hemangioma (n = 2), capillary hemangioma (n = 1), angiomyolipoma (n = 1)	Myxoidliposarcoma (n = 1)	Mesenchymal chondrosarcoma (n = 1)	Metastases of pulmonary adenocarcinoma (n = 1), papillary thyroid cancer (n = 1), and squamous cell carcinoma of the prostate (n = 1)
Intradural extramedullary (n = 22)	Hemangioblastoma (n = 3), neurinoma (n = 7), meningotheliomatous meningioma (n = 2), fibrous meningioma (n = 1), mixed meningioma (n = 3)	Clear cell meningioma (n = 1)	Papillary meningioma (n = 3), rhabdoid meningioma (n = 2)	–
Intramedullary (n = 5)	Mixopapillary ependymoma (n = 1), pilocytic astrocytoma (n = 1)	Protoplasmic astrocytoma (n = 1)	Plasma cell myeloma (n = 1), anaplastic ependymoma (n = 1)	–

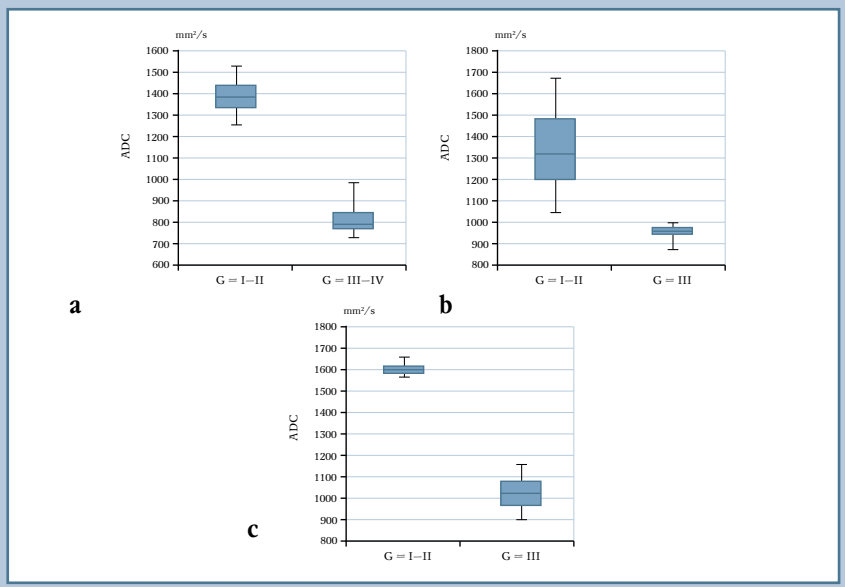

Fig. 2
Comparison of mean (M ± SD) apparent diffusion coefficient (ADC) values in different grade tumors: **a** – between extradural grade I–II/grade III–IV tumors (p = 0.008); **b** – between intradural extramedullary grade I–II/grade III tumors (p = 0.003); **c** – between intramedullary grade I–II/grade III tumors (p = 0.817)

and less than 1000 mm^2/s. The proliferative potential is known to be an essential factor for tumor growth, progression, aggressive behavior, and metastasis [20]. In this regard, assessment of the tumor proliferative potential in the preoperative period is of great value. Diffusion-weighted MRI with calculating the ADC allows the operating neurosurgeon, as early as at the preoperative preparation stage, to suppose the nature of tumor, choose the approach to patient management (the type and amount of surgery, degree of surgical aggression, use of fluorescence navigation, need for intraoperative neuromonitoring or chemoradiotherapy, etc.), and predict the outcome.

This study has its shortcomings. For example, this is a retrospective study with a low sample representation and a small number of analyzed malignant tumor forms for each of the groups. Studies in a larger number of patients and a comprehensive analysis of data for all types of spinal canal tumors are required for higher reliability of results.

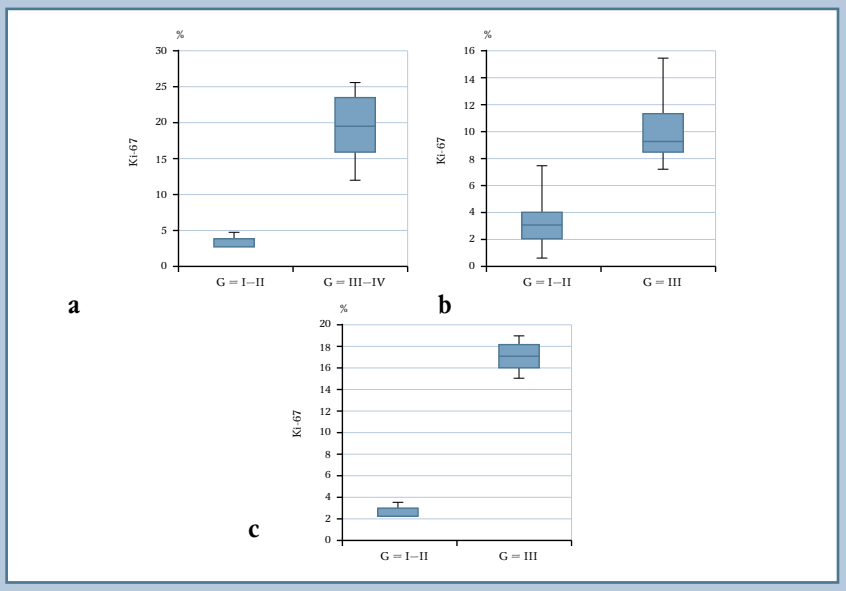

Fig. 3
Comparison of mean (M ± SD) Ki-67 index values in different grade tumors: **a** – between extradural grade I–II/grade III–IV tumors (p = 0.007); **b** – between intradural extramedullary grade I–II/grade III tumors (p = 0.002); **c** – between intramedullary grade I–II/grade III tumors (p = 0.633)

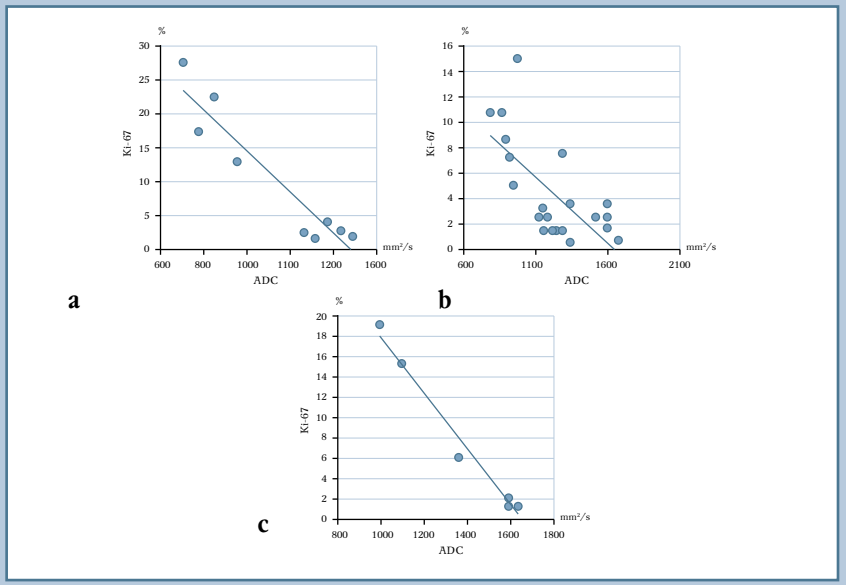

Fig. 4
Analysis of the correlation between apparent diffusion coefficient (ADC) values and the Ki-67 index: **a** – for extradural tumors (r = -0.88, p = 0.004); **b** – for intradural extramedullary tumors (r = -0.699, p = 0.0057); **c** – for intramedullary tumors (r = -0.77, p = 0.648)

Conclusion

The study has clearly demonstrated that ADC values and the proliferative activity index Ki-67 in extradural and intradural extramedullary tumors have significant differences. There is also a correlation between ADC and Ki-67 values for these tumor groups. Diffusion-weighted MRI with calculating the ADC can be used as an additional noninvasive technique for preoperative assessment of the proliferative potential of some spinal canal tumors.

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