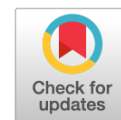


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# Показатели магнитно-резонансной томографии как радиомные маркеры в дооперационном определении степени злокачественности внеозговых образований

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## АННОТАЦИЯ

**Обоснование.** Внеозговые образования — одна из наиболее сложных групп для первичной дифференциальной диагностики. Определение радиомных маркеров и их стандартизация являются основными базовыми проблемами современного этапа развития медицины.

**Цель** — выявить радиомные маркеры для предоперационной оценки степени злокачественности внеозгового образования.

**Материалы и методы.** Ретроспективный анализ результатов исследований методом магнитно-резонансной томографии (1,5 Т) 156 пациентов с внеозговыми образованиями. Пациенты были разделены на 2 группы: (1) с наличием перифокальных изменений ( $n=106$ ) и (2) внеозговым образованием без перифокальных изменений ( $n=50$ ). В протокол сканирования были включены диффузионные и перфузионные последовательности. За зону интереса принимали (1) основной очаг и (2) зону перифокальных изменений. Выполнены измерения от основного очага и от зоны перифокальных изменений на картах измеряемого коэффициента диффузии,  $T2^*$ -контрастной перфузии (DSC), проведен анализ серий динамического контрастирования (DCE).

**Результаты.** Максимальный размер основного очага (узла) поражения в 1-й группе составил 2,2 см (1,4; 4,3), во 2-й группе — 1,2 см (0,9; 3,5); ограничение диффузии от основного очага поражения выявлено у 42 (39,6%) человек 1-й группы и у 7 (14%) — 2-й. Максимальный размер перифокальных изменений в 1-й группе составил 2,85 см (1,5; 4,7). Ограничение диффузии от периферической зоны выявлено в 52 (49,1%) случаях. У пациентов 1-й группы с верифицированной менингиомой ( $n=66$ ) путём многофакторного линейного регрессионного анализа выявлено, что максимальный размер основной зоны поражения увеличивал коэффициент объёмного кровотока (rCBF) от зоны перифокальных изменений в 3,3 раза ( $\beta$ coef. 3,3, ДИ 1,27; 5,28;  $p=0,003$ ), однако снижал показатель регионарного объёма крови (rCBV) в 4 раза ( $\beta$ coef. 4, ДИ -7,46; -0,71;  $p=0,02$ ).

**Заключение.** Перфузионные и диффузионные методы в сочетании с анатомическими последовательностями демонстрируют потенциал и могут выступать радиомическими маркерами при диагностике и лечении внеозговых образований. В дальнейшем наиболее перспективным выглядит выявление радиомических функциональных маркеров от зоны перифокальных изменений.

**Ключевые слова:** радиомика; внеозговое образование; менингиома; перифокальные изменения; степень злокачественности; диффузия; перфузия.

## Как цитировать

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# Use of magnetic resonance imaging features as radiomic markers in pre-operative evaluation of extra-axial tumor grade

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## ABSTRACT

**BACKGROUND:** Extra-axial tumors are one of the tumor groups with difficult primary differential diagnostics. Detection and standardization of radiomic markers are one of the main problems of our time.

**AIM:** To detect radiomic markers for preoperative assessment of extra-axial tumor grade.

**MATERIALS AND METHODS:** This study retrospective analyzed the magnetic resonance imaging (1.5 T) data of 156 patients with extra-axial tumors. Patients were divided into 2 groups: Group 1 ( $n=106$ ) with perifocal changes and Group 2 ( $n=50$ ) with extra-axial tumors without perifocal changes. Diffusion and perfusion sequences were included in the scanning protocol. The areas of interest include (1) the lesion and (2) the area of perifocal changes. Measurements were made from the lesion and the area of perifocal changes on ACD and DSC maps, DCE was analyzed.

**RESULTS:** The maximum lesion size in Group 1 was 2.2 cm (1.4; 4.3), whereas in 1.2 cm in Group 2 (0.9; 3.5). In Group 1, the diffusion restriction from the lesion was detected in 42 patients (39.6%), whereas 7 (14%) in Group 2. The maximum size of perifocal changes in Group 1 was 2.85 cm (1.5; 4.7). Diffusion restriction was detected in 52 (49.1%) cases. In Group 1, patients with verified meningioma multivariable linear regression analysis showed 3.3-times increase of rCBF of the maximum size of the lesion from the area of perifocal changes ( $\beta$ coef. 3.3, CI: 1.27; 5.28),  $p=0.003$ ; however, it demonstrated a 4-time decrease of rCBF ( $\beta$ coef. 4 CI: -7.46; -0.71),  $p=0.02$ .

**CONCLUSIONS:** Perfusion and diffusion methods combined with anatomical sequences show potential use as radiomic markers for diagnostic assessment and treatment of extra-axial tumors. Further detection of radiomic functional markers from the area of perifocal changes has potential.

**Keywords:** extra-axial tumors; meningioma; perifocal changes; malignancy grade; diffusion; perfusion.

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# 磁共振成像指标作为术前确定脑外组织恶性程度的放射标记物

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## 简评

**论证。**脑外结构是最难进行初级鉴别诊断的组之一。放射组标志物的测定及其标准化是现代医学发展阶段的主要基础问题。

**目标**是确定用于术前评估脑外肿块恶性程度的放射组标记。

**材料与方**回顾性分析使用磁共振成像 (1.5 T) 对 156 名脑外形成患者的研究结果。将患者分为 2 组: (1) 存在病灶周围改变 ( $n=106$ ) 和 (2) 无病灶周围改变的脑外肿块 ( $n=50$ )。扩散和灌注序列包括在扫描协议中。感兴趣的区域被定义为 (1) 主要焦点和 (2) 焦点周围变化的区域。从主焦点和测量扩散系数图上的焦周变化区域进行测量, T2\*-对比灌注 (DSC), 进行动态对比增强 (DCE) 系列分析。

**结果。**第 1 组主要病灶 (节点) 的最大尺寸为 2.2 厘米 (1.4; 4.3), 第 2 组为 1.2 厘米 (0.9; 3.5); 第 1 组 42 人 (39.6%) 和第 2 组 7 人 (14%) 检测到主要病灶扩散受限。第 1 组的最大焦周变化为 2.85 厘米 (1.5; 4.7)。在 52 例 (49.1%) 病例中检测到来自外周区的扩散受限。在第 1 组确诊脑膜瘤患者 ( $n=66$ ) 中, 多元线性回归分析显示, 主要病变区的最大尺寸使病灶周围变化区的体积血流系数 (rCBF) 增加了 3.3 倍 ( $\beta$  coef. 3.3, CI 1.27; 5.28;  $p=0.003$ ), 但将局部血容量 (rCBV) 降低了 4 倍 ( $\beta$  coef. 4, CI -7.46; -0.71;  $p=0.02$ )。

**结论。**灌注和扩散方法与解剖序列相结合显示出潜力, 可以作为诊断和治疗脑外病变的放射组学标志物。未来, 最有希望的是从焦周变化区域识别放射功能标志物。

**关键词:** 放射组学; 脑外教育; 脑膜瘤; 焦周变化; 恶性程度; 扩散; 灌注。

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## BACKGROUND

Medical images comprise huge amounts of information; therefore, radiomics in medicine has been actively developing in the last decade [1]. It looks promising to study texture analysis for differential diagnostics and functional analysis and to determine the disease prognosis [2]. Radiomics in oncology is the most demanded [3]. However, at the start of each work using a new diagnostic method, researchers face the problem of recognizing radiomic markers.

Extra-axial intracranial tumors are one of the least studied issues in neuroradiology, and meningiomas are the most common among them [4]. Different variants of meningiomas are described in detail in the literature [5]. Moreover, in ~15% of cases, atypical meningiomas of G2 or higher are detected [6]. Modern methods of pathomorphology help determine the grade by one criterion, namely, the presence of four mitoses in the field of view, which indicates the development of atypical meningioma [7]. However, the identification of radiomic markers and further work in this field may enable, within the framework of preoperative diagnostics, drawing a conclusion about the tumor grade, which will affect not only the approach of surgical intervention but also the improvement of treatment results.

In the presence of focal pathology, the radiologist should determine lesion genesis, assess the localization (intracerebral or extra-axial), and exert every effort to suggest the grade of tumor genesis. At the current stage of development in medicine, no exact tomographic criteria have been established to distinguish meningioma from similar pathologies, such as hemangiopericytoma [7] or solitary fibrous tumor of the dura mater. Thus, using the term “meningioma” in primary diagnostics of histologically unverified tumor is reasonable. In such cases, in clinical practice, when performing magnetic resonance imaging (MRI), it may be probably worth using the terms “extra-axial tumor” or “neoplasm of the meninges” according to the International Classification of Diseases. Possibly, the most important task in primary diagnostics of a tumor is not the determination of the histological type but the suggestion of the neoplasm grade.

This study aimed to identify radiomic markers for the preoperative assessment of the severity of malignancy of an extra-axial lesion.

## MATERIALS AND METHODS

### Study design

An observational single-center retrospective uncontrolled study was conducted.

### Inclusion criteria

The *inclusion criteria* were as follows: presence of an intracranial lesion with changes in the cortico-subcortical regions, results of a postoperative pathomorphological study,

and findings from diffusion-weighted imaging (DWI), dynamic contrast enhancement (DCE), and T2\*-contrast perfusion (DSC) in the scan protocol.

The *exclusion criteria* were as follows: absence of pathomorphological verification and absence of DCE and/or DSC in the scan protocol.

### Research conditions

A retrospective analysis of the MRI data of the cranial zone was performed. MRI examinations were performed from 2017 to 2021.

### Description of medical intervention

The MRI protocols of the cranial region were analyzed. All studies were performed on a Philips Achieva 1.5 T apparatus (Netherlands) using a multichannel head coil. In the MRI of the brain as part of the scanning protocol, the sequences of T2-weighted imaging (WI), T1-WI, fluid-attenuated inversion recovery (FLAIR), DWI (maximum b-factor 1000 s/mm<sup>2</sup>), followed by automatic mapping of the measured apparent diffusion coefficient (ADC), were analyzed.

*Contrasting technique.* The dose of the contrast agent was divided into two injections. DCE was performed at the first injection. Immediately after the DCE data collection, the second injection was performed, and T2\* dynamic susceptibility contrast (DSC) was collected. After DSC, without additional injection of a contrast agent, a T1-weighted 3D sequence was performed, followed by a T1 spin echo in the axial plane. When assessing perfusion, relative values were used (the ratio to a symmetrically located unchanged area in the opposite hemisphere).

*Image segmentation and identification of radiomic markers.* According to the data obtained, the main focus and zone of perifocal changes were segmented semi-automatically by an experienced radiologist (more than 15 years of experience in onco- and neuroradiology) and then measured on the ADC and DSC maps, including DCE analysis.

### Main study outcome

The primary endpoint was an extra-axial lesion identified on MRI.

### Additional study outcomes

The secondary endpoint was the qualitative assessment of the diffusion pattern according to DWI, results of the quantitative assessment of ADC values, assessment of the dynamic curve from the zone of perifocal infiltration, and assessment of perfusion maps.

### Subgroup analysis

The study participants were distributed into two groups: group 1 included patients with perifocal changes and group 2 (comparison group) included patients with extra-axial lesion without perifocal changes.

## Outcome registration methods

After MRI, all patients underwent surgical treatment and pathomorphological verification of the lesion.

## Ethical considerations

The paper analyzes the database of the institution. During hospitalization, all patients provided informed consent to the processing of personal data, including medical records, in the center to implement the educational process, scientific research, and publication in scientific literature, subject to medical secrecy.

## Statistical analysis

*Sample size calculation principles.* When planning and conducting the study, the sample size to achieve the required statistical power of the results was not calculated. In this regard, the sample of participants obtained during the study cannot be considered sufficiently representative; this prevents extrapolating the results and their interpretation to the general population of similar patients outside the study.

*Methods of statistical data analysis.* Stata 13 program (StataCorp LP, CollegeStation, TX, USA) was used for data analysis. The normality of the distribution of characteristics was assessed using the Shapiro–Wilk test. The equality of variances of the distribution of characteristics was calculated using the Levene test. For descriptive statistics of normally distributed characteristics with equality of variances, the mean values and standard deviations were calculated. Qualitative variables are presented as numbers (%), quantitative variables as median (25th and 75th percentile), unless otherwise indicated (Q1; Q3). A regression analysis was performed to identify predictor variables for a binary response variable using simple and multiple logistic regression scores. Proportional hazards regression was used to evaluate the relationship between one or more continuous or categorical variables before an adverse event. The significance level for all methods used was set as  $p < 0.05$ .

## RESULTS

### Study participants

According to the inclusion criteria, 156 patients were enrolled in the study. The mean patient age was  $50.63 \pm 6.41$  years.

All patients underwent surgical treatment after MRI, and pathomorphological verification of the lesion was performed. The patients were distributed into two groups: group 1 had perifocal changes ( $n = 106$ ), and group 2 had extra-axial lesion without perifocal changes ( $n = 50$ ). Pathological characteristics are presented in Table 1.

### Main results of the study

The maximum size of the main lesion (node) was 2.2 cm (1.4–4.3) in group 1 and 1.2 cm (0.9–3.5) in group 2.

**Table 1.** Pathomorphological characteristics of the lesions

Pathological characteristics	Number of patients, $n$
Encephalomyelitis	2
Metastatic lesion (breast cancer or lung cancer)	30
Typical meningiomas G1	100
Atypical meningiomas G2–3	16
Hemangioblastoma G1	1
Neurinoma G1	7

Restriction of diffusion from the main lesion was detected in 42 (39.6%) patients in group 1 and in 7 (14%) patients in group 2.

The maximum size of perifocal changes in group 1 was 2.85 cm (1.5–4.7). Diffusion restriction from the peripheral zone was detected in 52 (49.1%) cases.

In group 1, the ADC value was determined from both the detected focus and the zone of perifocal changes in various pathologies (Table 2). The ADC value from the brain tissue adjacent to the node in group 2 was  $0.71 \pm 0.07 \times 10^{-3} \text{ mm}^2/\text{s}$ .

In group 1, a multivariate linear regression analysis revealed that in patients with verified meningioma ( $n = 66$ ), the maximum size of the main lesion zone increased the coefficient of volumetric regional cerebral blood flow (rCBF) from the zone of perifocal changes by 3.3 times ( $\beta$ coef. 3.3; confidence interval 1.27–5.28),  $p = 0.003$  (Fig. 1); however, it reduced the cerebral blood volume (rCBV) by four times ( $\beta$ coef. 4; CI  $-7.46$  to  $-0.71$ ),  $p = 0.02$  (Fig. 2).

The analysis of DCE values in group 2 did not reveal a correlation between the tumor size and DCE from the area of perifocal changes, in contrast to perfusion maps (Fig. 3).

### Additional research results

To introduce the work results into the clinical practice in case of newly diagnosed extra-axial lesion, an algorithm for using MRI techniques was proposed (Fig. 4).

### Adverse events

No adverse events occurred.

## DISCUSSION

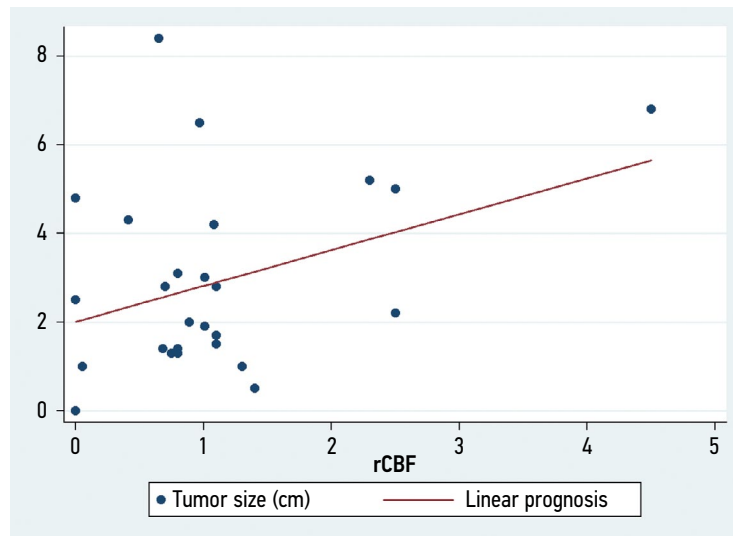
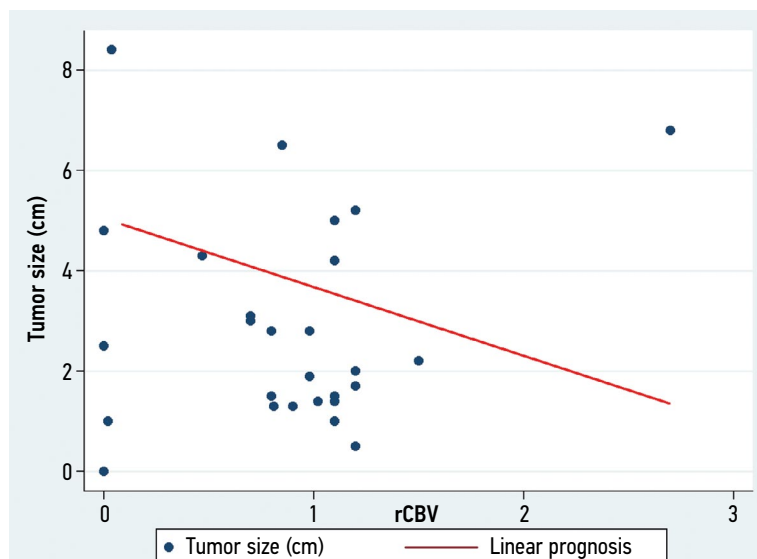
Radiomic markers help obtain new results from long-used medical images. Moreover, radiomics is a recently emerging and rapidly developing area. Currently, all works are focused on the segmentation of the main tumor focus. However, in the world literature, no studies have investigated tissue characteristics around the lesion.

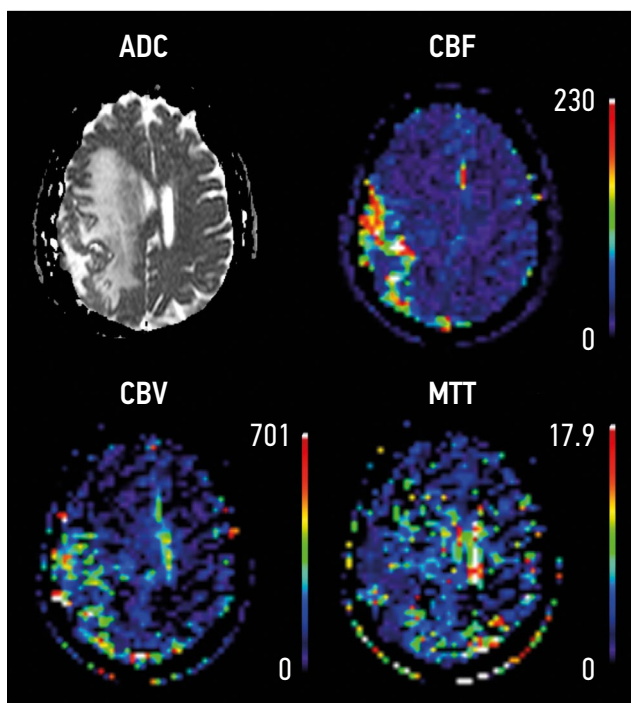
Gliomas are the most studied area in neuroradiology. A study discussed the results of the assessment of perifocal changes in gliomas [8], where tumor infiltration is formed

**Table 2.** Perfusion and diffusion values of perifocal changes for various brain pathologies in group 1

Brain pathology	ADC ( $\times 10^{-3}$ mm <sup>2</sup> /s)		DSC relative to the contralateral hemisphere		DCE	
	From the node	From perifocal changes	From the node	From perifocal changes	From the node	From perifocal changes
Typical meningioma G1	1.52 $\pm$ 0.95	1.78 $\pm$ 0.73	Unaltered, may be slightly increased	Unaltered or decreased	Various	Various
Atypical meningioma G2–G3	0.72 $\pm$ 0.05	1.13 $\pm$ 0.86	Increase in rCBF, decrease in rCBV	Increase in rCBF, decrease in rCBV	Various	Various
Metastasis	1.03 $\pm$ 0.15	1.55 $\pm$ 0.23	Increased	Unaltered or decreased	Various	Unaltered, no early accumulation
Neurinoma	1.2 $\pm$ 0.04	1.56 $\pm$ 0.06	Unaltered or decreased	Unaltered or decreased	Unaltered, no early accumulation	Unaltered, no early accumulation
Abscess	0.63 $\pm$ 0.04	1.26 $\pm$ 0.06	Decreased	Unaltered or decreased	No early accumulation	Unaltered, no early accumulation

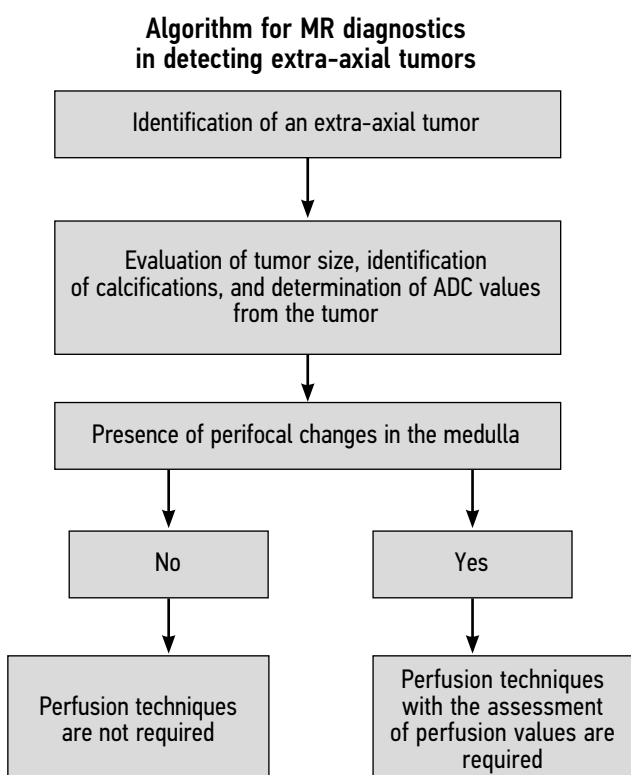
Note. ADC, apparent diffusion coefficient; DSC, T2\* perfusion; DCE, dynamic contrast enhancement.

**Fig. 1.** Linear regression analysis: relation between tumor size and CBF rate**Fig. 2.** Linear regression analysis: relation between tumor size and CBV rate



**Fig. 3.** Atypical meningioma: ADC — apparent diffusion coefficient; CBF — cerebral blood flow, CBV — cerebral blood volume, MTT — mean transit time.

around the glial tumor. Moreover, perifocal changes in extra-axial tumors have been under-investigated. We managed to find a very limited number of studies that have investigated perifocal changes in extra-axial lesions [9].



**Fig. 4.** Algorithm for MR-diagnostics of primarily detected extra-axial tumors.

In addition, the indicators used in radiomics are not standardized, as are the MRI sequences used, which makes both the process and the results difficult to replicate and scale. Very few studies have investigated effective radiomic markers.

**Summary of the main results**

In this study, indicators that are the most promising for use in the further development of radiomics were investigated. These indicators include DWI, ADC values, and perfusion parameters. A multivariate linear regression analysis of the correlation of indicators was performed (CI  $-7.46$  to  $-0.71$ ),  $p = 0.02$  (Fig. 2).

Analysis of DCE values in group 2 did not reveal a correlation between tumor size and DCE values.

**Discussion of the main results**

In clinical practice, to detect an extra-axial neoplasm through MRI, not only the structure of the neoplasm should be assessed, but precise perifocal changes must be identified or ruled out since in our studies of patients without perifocal changes, not a single malignant meningioma was detected. Thus, the result of this study demonstrates that the absence of perifocal changes virtually excludes the malignancy of the lesion detected.

In clinical practice, to rule out perifocal changes in the presence of an extra-axial lesion, it is sufficient to use FLAIR as a sequence in which infiltrative or edematous changes become the most demonstrative. The absence of perifocal changes does not guarantee the absence of atypia in this tumor; just as in the presence of perifocal changes, an atypical morphological presentation will not always be obtained. However, because of the complexity of differential diagnostics and the absence of direct criteria indicating atypia, there is a pronounced need to use all criteria, including indirect ones. A set of indirect criteria in most cases will determine the decision of the radiologist.

To detect perifocal changes on MRI, it is important to assess their genesis (ischemia, vasogenic or cytotoxic edema, and infiltration). To date, DWI is used in every brain scan protocol. Ischemic brain changes in DWI have been evaluated in detail in contrast to perifocal changes in extra-axial lesions. In differential diagnostics of the changes, it is important to analyze not only the presence of diffusion restriction but also the ADC maps. This is required primarily to eliminate the effect of T2 transillumination and avoid false-positive results and, secondly, to determine the ADC value.

The results of this study revealed that different ADC values were obtained from both the node and perifocal changes. The ADC value from the adjacent medulla in the presence of an extra-axial tumor, but in the absence of perifocal changes, was  $0.71 \pm 0.07 \times 10^{-3} \text{ mm}^2/\text{s}$ . The significant difference in the ADC values from the medulla and from perifocal changes in meningiomas is prognostically interesting in terms of its consideration for preoperative assumptions about the grade.

In our opinion, an important limiting factor affecting the ACD value is the presence of calcifications in the tumor, since they will distort the value or completely prevent its adequate calculation. However, the presence of calcifications in a meningioma is a clear sign of the absence of growth in it; as a result, the development of cell atypia becomes even less probable [10].

We also performed MR perfusion. In the present study, to analyze the identified changes, two types of MR perfusion using a contrast agent were employed, namely, DSC and DCE. Studies have described the use of perfusion techniques in various pathologies [11, 12]. In brain examination, DCE can be included in the scanning protocol to assess the vascular wall permeability [13, 14].

According to the literature, the use of perfusion methods appears appropriate in the differential diagnostics of typical and atypical meningiomas. However, according to our results and those of several authors, evaluating perifocal changes is important to make an adequate decision about the expected grade [15].

A study reported that the greatest increase in perfusion values relative to the opposite hemisphere will be registered in cases of angiomatous meningioma [15] and atypical meningioma, which was also demonstrated in our work.

With further case follow-up and absence of histological verification, in our opinion, the proposed algorithm can be applied with a mandatory assessment of the tumor growth and the emergence/growth of perifocal changes.

In case of a history of histological verification, the use of perfusion techniques is not required in a typical meningioma ( $G = 1$ ). In this case, to assess continued growth or recurrence, contrast enhancement without perfusion protocols is sufficient; however, the need to assess atrophic changes in the medulla in the site of surgical intervention should be considered. When meningioma atypia is confirmed ( $G = 2-4$ ), perfusion techniques are necessary to assess the dynamics of changes. In the dynamic study of atypical meningiomas,

it is important to consider the type of surgical treatment performed, such as surgical removal, radiation therapy, and embolization of tumor afferents, etc. This approach is similar to the glioma monitoring protocol.

With an increase in the tumor size and presence of perifocal changes, the need to assess the perfusion maps in correlation with the ACD value as a predictor of the severity of malignancy is clear.

### Study limitations

Our results on DCE indicate that the issue of using DCE to assess the severity of malignancy of an extra-axial lesion in clinical practice remains open and requires further investigation.

## CONCLUSION

Perfusion and diffusion methods combined with anatomical sequences demonstrate potential and can be used as radiomic markers in the diagnostics and treatment of extra-axial lesions. In the future, the identification of radiomic functional markers from the zone of perifocal changes is the most promising.

## ADDITIONAL INFORMATION

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**Competing interests.** The authors declare that they have no competing interests.

**Authors' contribution.** T.A. Bergen, I.A. Soynov — research concept and design, processing and analysis, writing the manuscript; M.G. Pustovetova — processing and analysis, writing the manuscript. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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