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Apparent diffusion coefficient in the evaluation of cerebral gliomas malignancy

Difuzioni koeficijent u proceni stepena maligniteta cerebralnih glioma

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Abstract

Background/Aim. Magnetic resonance imaging (MRI) is a key modality not only for lesion diagnosis, but also to evaluate the extension, type and grade of the tumor. Advanced MRI techniques provide physiologic information that complements the anatomic information available from conventional MRI. The aim of this study was to determine whether there is a correlation between apparent diffusion coefficient (ADC) maps of intracranial glial tumors and histopathologic findings and whether ADCs can reliably distinguish low-grade from high-grade gliomas. **Methods.** This retrospective study included 25 patients with MRI examination up to seven days before surgery, according to the standard protocol with the following sequences: T1WI, T2WI, FLAIR, DWI and post contrast T1WI. Data obtained from DW MRI were presented by measuring the value of ADC. The ADC map was determined by utilizing Diffusion-Perfusion (DP) Tools software. All the patients underwent surgical resection of the tumor. Histological diagnosis of tumors was determined according to the World Health Organization (WHO) classification. The ADC values were compared with the histopathologic findings according to the WHO criteria. **Results.** The ADC values of astrocytomas grades I (0.000614 ± 0.000032 mm^2/s) were significantly higher (< 0.001) than the ADC values of anaplastic astrocytomas (0.000436 ± 0.000016 mm^2/s) and the ADC values of glioblastomas multiforme (0.000070 ± 0.000008 mm^2/s). The ADC values of astrocytomas grades II (0.000530 ± 0.000114 mm^2/s) were significantly higher (< 0.001) than the ADC values of anaplastic astrocytomas (0.000436 ± 0.000016 mm^2/s) and glioblastomas multiforme (0.000070 ± 0.000008 mm^2/s). The ADC values of anaplastic astrocytomas (0.000436 ± 0.000016 mm^2/s) were significantly higher (< 0.001) than the ADC values of glioblastomas multiforme (0.000070 ± 0.000008 mm^2/s). The ADC values in the cystic part of the tumor for astrocytomas grades I (0.000775 ± 0.000023 mm^2/s) were significantly higher (< 0.001) than the ADC values of anaplastic astrocytomas (0.000119 ± 0.000246 mm^2/s) and glioblastomas multiforme (0.000076 ± 0.000004 mm^2/s). The ADC values astrocytomas grades II (0.000511 ± 0.000421 mm^2/s) were significantly higher (< 0.001) than the ADC values of glioblastomas multiforme (0.000076 ± 0.000004 mm^2/s). **Concluson.** DWI with calculation of ADC maps can be regarded as a reliable useful diagnostic tool, which indirectly reflects the proliferation and malignancy of gliomas. The ADCs maps can both predict the results of histopathological tumor and distinguish between low- and high-grade gliomas, and provide significant information for presurgical planning, treatment and prognosis for patients with high-grade astrocytomas.

Key words:
glioma; diffusion magnetic resonance imaging; diagnosis; neoplasm staging.

Apstrakt

Uvod/Cilj. Magnetna rezonanca (MRI) je ključni modalitet ne samo za dijagnostiku lezija, već i za procenu tipa i gradusa tumora i stepena širenja u okolno tkivo. Savremene MRI tehnike, kao što je *diffusion-weighted imaging* (DWI), obezbeđuje fiziološke informacije o tumoru, dopunjujući anatomske informacije dobijene na konvencionalnom MRI. Cilj naše studije bio je da se utvrdi da li postoji korelacija mape prividnog difuzionog koeficijenta (ADC) i patohistološkog nalaza, i da li ADC koeficijent može napraviti razliku između niskogradusnih i visokogradusnih glioma. **Metode.** Ovom retrospektivnom studijom bilo je obuhvaćeno 25 bolesnika, kod kojih je urađen MRI pregled do sedam dana pre operacije, prema standaradnom protokolu sa sledećim sekvencama: T1WI, T2WI, FLAIR, DWI i postkontrastna T1WI. Podaci dobijeni od DW MRI predstavljeni su merenjem vrednosti ADC koeficijenta. ADC mapa je određivana korišćenjem *Diffusion-Perfusion* (DP) *Tools* softvera. Svi bo-

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lesnici bili su podvrgnuti hirurškoj resekciji tumora. Histološka klasifikacija tumora izvršena je prema kriterijumima Svetske zdravstvene organizacije. Dobijene ADC vrednosti upoređivane su sa patohistološkim nalazom tumora. **Rezultati.** Vrednost ADC koeficijenta astrocitoma gradus I (0,000614 ± 0,000032 mm^2/s) bila je statistički značajno viša (< 0,001) od vrednosti ADC koeficijenta anaplastičnog astrocitoma (0,000436 ± 0,000016 mm^2/s) i glioblastoma multiforme (0,000070 ± 0,000008 mm^2/s). Vrednosti ADC koeficijenta astrocitoma gradusa II (0,000530 ± 0,000114 mm^2/s) bila je statistički značajno viša (< 0,001) od vrednosti ADC koeficijenta anaplastičnog astrocitoma (0,000436 ± 0,000016 mm^2/s) i glioblastoma multiforme (0,000070 ± 0,000008 mm^2/s). Vrednosti ADC koeficijenta anaplastičnog astrocitoma (0,000436 ± 0,000016 mm^2/s) bila je statistički značajno viša (< 0,001) od vrednosti ADC koeficijenta glioblastoma multiforme (0,000070 ± 0,000008 mm^2/s). Astrocitom gradusa I (0,000775 ± 0,000023 mm^2/s) imao je vrednost ADC koeficijenta cisticnog dela tumorskog tkiva statistički značajno višu (< 0,001) od vrednosti ADC anaplastičnog astrocitoma (0,000119 ± 0,000246 mm^2/s) i glioblastoma multiforme (0,000076 ± 0,000004 mm^2/s). Vrednost ADC koeficijenta astrocitoma gradusa II (0,000511 ± 0,000421 mm^2/s) je bila statistički značajno viša (< 0,001) od vrednosti ADC koeficijenta glioblastoma multiforme (0,000076 ± 0,000004 mm^2/s). **Zaključak.** DWI sa određivanjem ADC mape može se smatrati pouzdanim dijagnostičkim sredstvom koje posredno odražava proliferaciju i malignitet glioma. Vrednost ADC mape može predvideti histopatološke rezultate tumora, razlikovati niskogradusne od visokogradusnih glioma, ali i pružiti značajne informacije za prehirurško planiranje, lečenje i prognozu bolesnika sa visokogradusnim astrocitomima.

Ključne reči:
gliom; magnetna rezonanca, difuziona; dijagnoza; neoplazme, određivanje stadijuma.

Introduction

'The first application of magnetic resonance imaging (MRI) in the early 1980s radically changed the radiographic diagnosis of primary and secondary brain tumors. MRI is a key modality not only for lesion diagnosis, but also to evaluate the extension, type and grade of the tumor. Advanced MRI techniques such is diffusion weighted imaging (DWI) provide physiologic information that complements the anatomic information available with conventional MRI [1]. In recent years the increasing number of the world's researches has been focused on proving the fundamental and practical importance of DWI and apparent diffusion coefficient (ADC) and the possibility of using the results in tumor grading, determination of tumor cellularity, to differentiate tumor and perifocal edema and especially emphasizes the possible ability to predict response to applied treatment of tumor [2]. There appears to be a correlation between the apparent diffusion coefficient values on the one hand and tumor cellularity and tumor grade on the other [3]. Research data on intracranial tumors indicate that high ADC values were attributable to low cellularity, necrosis or cysts, and lower values to dense, highly cellular tumor [4].

The aim of this study was to determine whether there is a correlation between ADC maps of intracranial glial tumors and histopathologic findings and whether ADC values can reliably distinguish low- grade from high-grade gliomas.

We have hypothesized that the ADC value can make the difference between low and high grades gliomas, and ADC value ratio can predict the histoapthological results of tumros.

Methods

A retrospective study involved a group of 25 patients with histologically proven intracranial gliomas. MRI examination was performed on the Siemens Avanto MR device (Erlangen, Germany) with magnetic field of 1.5 Tesla (T). The examinations were performed in all the patients, up to seven days before surgery, according to the standard protocol with the following sequence: T1WI, T2WI, FLAIR, DWI and post contrast T1WI. All the patients underwent surgical resection of the tumor. Histological diagnosis of tumors was determined according to the World Health Organization (WHO) classification.

Data obtained from DWI MRI were presented by measuring the value of ADC coefficients. The ADC map was determined by utilizing DP Tools software (Figure1). Based on the typical MR output, data in terms of localization, size and morphological characteristics of the tumor were determined; based on the quantity of DWI MRI values and its degree of malignancy (biological potential) was established. The ADC values were compared with the histopathologic findings according to the WHO criteria.

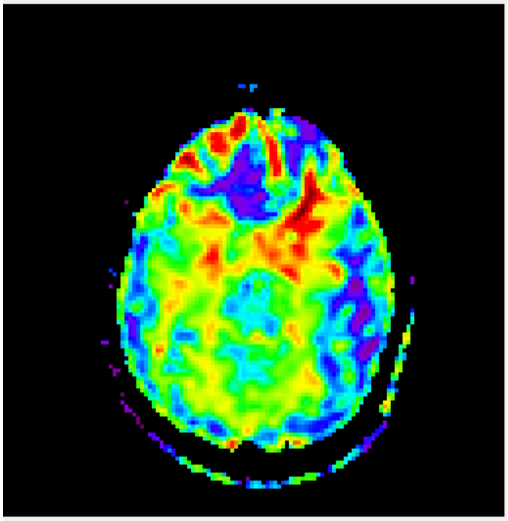

Fig. 1 – Apparent diffusion coefficients (ADC) map of patients with glioblastoma multiforme.

For registration, grading, grouping, graphical and tabular representation of the data, Microsoft Excel 2003 software was utilized. The results were analysed by SPSS software, version 10.0. Within this analysis the statistical boundary of an error was within 0.05 (5%). The following statistical pa-

rameters were shown: arithmetic mean ($\bar{x}$), standard deviation (SD), median, minimal value, maximum value and index of structure (%). By comparing the values of DWI and ADC among different patients that were researched with pathological diagnostics, analysis of variance (ANOVA) and Dunnett *post hoc* test were performed. The correlation was carried out by quantitative comparison of the vales of ADCs with the degree of malignancy, and the DWI MR diagnosis with definite histopathological diagnosis of brain tumors.

Results

Out of 25 patients with gliomas included in the study 15 (60%) were men and 10 (40%) women. Malignancy of the tumor was graded by WHO I–IV. The diagnosis of the tumor was astrocytoma grade I (2 patients), astrocytoma grade II (5 patients), anaplastic astrocytoma (5 patients), glioblastoma multiforme (13 patients) (Table 1).

The average age of all the patients was 50.40 ± 12.53 years. The youngest patient had 19 and the oldest ones 77 years. The patients with glioblastoma multiforme (54.08 ± 2.83 years) and anaplastic astrocytomas (52.00 ± 9.59 years) were older those with the astrocytoma grade I (49.00 ± 2.83 years) and astrocytoma grade II (39.80 ± 9.63 years) (Table 2).

The ADC values of astrocytomas grade I (0.000614 ± 0.000032 mm^2/s) were significantly higher (< 0.001) than the ADC values of anaplastic astrocytomas (0.000436 ± 0.000016 mm^2/s) and ADC values of glioblastomas multiforme (0.000070 ± 0.000008 mm^2/s) (Tables 3 and 4). The ADC values of astrocytomas grade II (0.000530 ± 0.000114 mm^2/s) were significantly higher (< 0.001) than the ADC values of anaplastic astrocytomas (0.000436 ± 0.000016 mm^2/s) and glioblastomas multiform (0.000070 ± 0.000008 mm^2/s). The ADC values of anaplastic astrocytomas (0.000436 ± 0.000016 mm^2/s) were significantly higher (< 0.001) than ADC values of glioblastomas multiform (0.000070 ± 0.000008 mm^2/s).

Table 1

Distribution of patients compared to histopathological diagnosis and sex

Histopathological diagnosis	Sex, n (%)		Total
	men	woman	
Astrocitomas grades I	2 (8)	–	2 (8)
Astrocytomas grades II	3 (12)	2 (8)	5 (20)
Anaplastic astrocytomas	4 (16)	1 (4)	5 (20)
Glioblastoma multiforme	6 (24)	7 (28)	13 (52)
Gliomas total	15 (53.6)	10 (31.3)	25 (100)

Table 2

Distribution of the patients compared to histopathological diagnosis and age

Histopathological diagnosis	Age (years)				
	$\bar{x}$	SD	med	min	max
Astrocitomas grades I	49.00	2.83	49.00	47.00	51.00
Astrocytomas grades II	39.80	9.63	43.00	29.00	52.00
Anaplastic astrocytomas	52.00	19.56	61.00	24.00	72.00
Glioblastoma multiforme	54.08	9.59	55.00	38.00	77.00
Gliomas total	50.40	12.53	51.00	24.00	77.00

$\bar{x}$ – arithmetic mean; SD – standard deviation; min – minimal value; max – maximal value; med – mediana.

Table 3

The value of apparent diffusion coefficients (ADC) of the solid part of the tumor in comparison with histopathological diagnosis

Histopathological diagnosis	ADC (mm^2/s)				
	$\bar{x}$	SD	med	min	max
Astrocitomas grades I	0.000614	0.000032	0.000636	0.000565	0.000645
Astrocytomas grades II	0.000530	0.000114	0.000510	0.000222	0.000671
Anaplastic astrocytomas	0.000436	0.000016	0.000432	0.000412	0.000462
Glioblastoma multiforme	0.000070	0.000008	0.000069	0.000059	0.000082
Gliomas total	0.000491	0.000160	0.000495	0.000059	0.000671

$\bar{x}$ – arithmetic mean; SD – standard deviation; min – minimal value; max – maximal value; med – mediana.

Table 4

Comparison of the apparent diffusion coefficients (ADC) values of the solid part of the tumor between the different histologic diagnosis (ANOVA and Bonferroni post-hoc test - *p*)

Histopathological diagnosis	Astrocitomas grades II	Astrocitomas grades III	GBM
Astrocitomas grades I	0.0018	< 0.001	< 0.001
Astrocitomas grades II		0.001	< 0.001
Astrocitomas grades III			< 0.001

GBM – glioblastoma multiforme.

The ADC values in the cystic part of tumor for astrocytomas grade I (0.000775 ± 0.000023 mm^2/s) were significantly higher (< 0.001) than the ADC values of anaplastic astrocytomas (0.000119 ± 0.000246 mm^2/s) and glioblastomas multiforme (0.000076 ± 0.000004 mm^2/s) (Tables 5 and 6). The ADC values of astrocytomas grade II (0.000511 ± 0.000421 mm^2/s) were significantly higher (< 0.001) than the ADC values of glioblastomas multiforme (0.000076 ± 0.000004 mm^2/s).

Discussion

Astrocytomas are the most common primary brain neoplasms in adults and account for more than 70% of all gliomas. The WHO Grades III and IV malignant astrocytomas include anaplastic astrocytoma and glioblastoma multiforme and are the most prevalent astrocytomas, with the annual incidence of 3–4 per 100.000. At least 80% of malignant gliomas are glioblastoma [5]. Anaplastic astrocytoma and glioblastoma tend to invasion of the surrounding brain. Histopathological studies found malignant cells in macroscopically unsuspicious brain parenchyma remote from the primary tumor, even affecting the contralateral hemisphere. In early stages, diffuse interneural infiltration with changes of the ADC occurs. Only about 2% of patients with high-grade brain tumors survive the first 5 years after diagnosis. One of the main factors for the poor prognosis of glioblastomas is the invasiveness of malignant cells. These infiltrating glioma cells can hardly be imaged by standard techniques [6].

Conventional MRI can display the anatomical appearance of brain tumor, but fails to provide physiologic and functional information that is crucial for tumor grading, predicting clinical outcome and response to therapy [7]. Advanced MRI technics such as quantitative DWI, which utilizes the Brownian motion of water molecules, has been shown to be able to provide information [8] at the cellular or physiologic level [9] about cellular density and properties of the extracellular matrix. Because extracellular water molecules move more freely than those in the intracellular spaces, the ADC value calculated from DWI can serve as a marker of cellularity [8]. ADC is a direct reflection of tumor cell density [10]. This potential biomarker can be obtained without any radiation hazard or contrast media in only few minutes, and has been proven to be effective in predicting and monitoring the treatment of various cancers [8].

It is believed that ADC can be an important diagnostic and prognostic biomarker as it is thought to be inversely proportional and correlated with cellularity and tumor malignancy [8, 9]. So it indicates that the most aggressive and most cellularity places within heterogeneous tumors, which are prognostic essential, correspond to the minimum ADC value [9]. For now, have also been spotted some limitations of the DW such as: poor spatial resolution, the inability to eliminate certain artefacts (eg. skull base bone, the air in the sinus cavities) and there are some changes in ADC values in the presence of hemorrhagic, necrotic and cystic fields. Strength matches and mismatches with the ADC map also affect the furthest outcome measurements and results [9].

ADC values of some tumors are inversely related to cellularity and the ratio of nuclear area to total cytoplasm, and thus decreased ADCs may be found in some aggressive tumors. Differences in ADCs likely reflect differences in cellularity and density, nuclear-to-cytoplasmic ratio, extracellular matrix, and edema. For instance, a low ADC value is the result of reduced extracellular water motion within the crowded interstitium of a hypercellular area, or from impeded intracellular water motion within cells of a high nuclear-to-cytoplasmic ratio. Gliomas have been found to have ADC values inversely correlated to cell density and the ratio of nuclear area to total cytoplasm, with lower values correlating with more aggressive tumor. ADC can accurately predict tumor behavior and monitor treatment responses with standardized protocols [11]. A functional diffusion map, made by mapping the changes in ADC values potentially reflects cellularity, as a predictive biomarker for the anti-angiogenic treatment of malignant gliomas. Hypercellular regions defined by the functional diffusion map

Table 5

Apparent diffusion coefficients (ADC) value of the cystic part of the tumor in comparison with histopathological diagnosis

Histopathological diagnosis	ADC (mm^2/s)				
	$\bar{x}$	SD	med	min	max
Astrocitomas grades I	0.000755	0.000023	0.000761	0.000701	0.000789
Astrocytomas grades II	0.000511	0.000421	0.000640	0.000000	0.000992
Anaplastic astrocytomas	0.000119	0.000246	0.000000	0.000000	0.000604
Glioblastoma multiforme	0.000076	0.000004	0.000075	0.000071	0.000081
Gliomas total	0.000446	0.000396	0.000598	0.000000	0.000992

$\bar{x}$ – arithmetic mean; SD – standard deviation; min – minimal value; max – maximal value; med – mediana.

Table 6

Comparison of the apparent diffusion coefficients (ADC) values of the cystic part of the tumor between the different histologic diagnosis (ANOVA and Bonferroni *post-hoc* test – *p*)

Histopathological diagnosis	Astrocitomas grades II	Astrocitomas grades III	GBM
Astrocitomas grades I	0.106	< 0.001	< 0.001
Astrocitomas grades II		0.017	< 0.001
Astrocitomas grades III			0.999

GMB – glioblastoma multiforme.

were shown to be predictive of tumor progression. Patients with persistent diffusion restriction demonstrated better survival, which was explained by atypical necrosis [8].

A lower value of ADC indicates highly malignant gliomas, and high ADC value corresponds to low grades astrocytomas, as evidenced in the results of previous studies [12]. Our findings are in accordance with the previously reported. Barajas et al. [13] suggest that while ADC measurements correlate with tumor cell density, DWI is a more accurate predictor of clinical outcome, given the capacity of this technique to summate additional unidentified prognostic biologic features of tumor aggressiveness beyond cell density. Several other studies have demonstrated change in post-therapeutic ADC values following radiation and chemotherapy in primary glial brain tumors [13].

The ADC has been found to have an inverse relation with the grade of astrocytomas. Lower ADC values suggest a malignant high-grade astrocytoma, whereas higher ADCs suggest low-grade astrocytoma. On the basis of specific histologic features of the tumor, such as cellularity, nuclear atypia, mitosis, pleomorphism, vascular hyperplasia, and necrosis, the revised WHO classification subdivides gliomas into four grades. Among mean ADC, minimum ADC, and maximum ADC values, minimum ADC value was the strongest prognostic factor in glioblastoma multiforme (GBM) patients for overall survival [14]. Brasil Caseiras et al. [15] distinguished low-grade gliomas (grade II astrocytomas) as having no effect on prognosis with respect to ADC values. None of the ADC parameters proved to be a useful predictor of malignant transformation in low-grade gliomas. Low ADC values, independent of tumor grade, correlate with poor survival in malignant astrocytomas. Pretreatment DWI with calculation of ADC values may be helpful for planning therapy and in prognostication for patients with high-grade astrocyotomas [14].

A study conducted by Yin et al. [16] showed that the ADC values were inversely correlated to the degree of malignancy of gliomas, namely that high grade gliomas had significantly lower ADC and relative ADC (rADC) values in relation to gliomas categorized as low grade. Also, Ristić-Baloš et al. [17] reported that DWI can be useful in differentiating benign and malignant tumors from normal parenchyma and in grading gliomas. The results of our research correspond with previous findings from the literature that glial tumors grade II and grade III showed a statistical significance. In the patients with anaplastic astrocytoma, values of ADC were between glioblastom (GBM) and astrocytoma grade II. Our findings are in accordance with the previously reported [18–20].

In a series of 20 patients with histologically proven gliomas, the ADC value of high grade gliomas was significantly lower than the value of low- grade gliomas [21], which coincides with our results. The lower ADC value of GBM compared to low-grade astrocytomas was observed in a series of 56 patients with intracranial tumors [22]. In our study, the ADC value of the GBM was significantly lower than the ADC value of astrocytoma grade I. Qualitative assessment of the ADC map shows low signal in the contrast discolorated area compared to the no-discolorated peritumoral and edema in high- grade gliomas [23]. However, some researchers argue that the ADC map helps in differentiating tumors from the normal brain tissue and grading of malignant neoplasms, but it is impossible to distinguish between malignant and benign tumors [24].

Some researchers argue that there is a considerable overlap of ADC values of the normal brain tissue and those of high- and low- grade neoplasms raising the question of their utility in individual patients [22, 25]. However, Lam et al. [26], based on their research, found that there was no significant difference between the grade of the tumor based on ADC values. DWI can be used for assessment of glioma invasion and detection of necrotic tumor. There is also a correlation between ADC values after surgery with postoperabtive radiotherapy and survival time in patients with glioblastoma. A significant shorter median survival time has been shown for patients with low ADC values within residual T2 hyperintense zone [24].

Conclusion

ADC values of tumor parenchyma can indirectly reflect the proliferation and malignancy of gliomas. ADC maps can distinguish low- and high-grade gliomas, and ADC values can predict the results of histopathological findings.

Therefore, DWI with calculation of ADC maps can be regarded as reliable useful diagnostic tools which provide useful information not only for the diagnosis and grading of gliomas, but also for presurgical planning, treatment and prognosis for patients with high-grade astrocytomas.

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