

Anaplastic transformation of low-grade gliomas (WHO II) on magnetic resonance imaging

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Abstract

Introduction: Malignant transformation among gliomas WHO II ranges between 35% and 89%. However, according to some reports, all gliomas WHO II undergo such transformation over time. The aim of the study was to analyse MRI parameters indicating anaplastic transformation of gliomas WHO II.

Material and methods: Forty-six consecutive patients were enrolled in the study (20 females and 26 males; range of age 36 ± 9 years) with supratentorial glioma WHO II. Multiparametric MR examination included morphological imaging, perfusion-weighted imaging, diffusion-weighted imaging and proton magnetic resonance spectroscopy. Group division depended on the course of disease (ST – stable group, AT – anaplastic transformation group).

Results: Subtotal tumour resection was achieved in the whole AT group, whereas in the ST group, total tumour resection was achieved in 10/29 (34%) patients. The size of the residual tumour after surgery was statistically significantly higher in the AT group compared to the ST group (AT: $51.5 \text{ cm}^3 \pm 37.7$ vs. ST: $29.0 \text{ cm}^3 \pm 37.9$; $p = 0.011$). Contrast enhancement in the AT group occurred in 5/11 (45%) of tumours and in none of the patients' areas of contrast enhancement were resected during surgery/biopsy. However, the initial MR showed contrast enhancement in 10/29 (34%) of patients in the ST group. The areas of contrast enhancement were totally resected in all patients. Compared to the ST group tumours that underwent anaplastic transformation had statistically significantly higher values of mean nrCBV and max nrCBV on the initial MR, the follow-up and final MR examinations. However, statistically significant differences between the groups in ADC values were observed on the follow-up and final MR whereas mean Cho/Cr and mean Cho/NAA were observed as late as on the final MR examination.

Conclusions: Multiparametric MR examination allows the detection of LGGs with high probability of rapid anaplastic transformation and the detection of transformation prior to the occurrence of contrast enhancement. The value of nrCBV is the most useful in the diagnosis of anaplastic transformation. The resection of contrast enhancement area of the tumour significantly increases time to anaplastic transformation of LGGs.

Key words: anaplastic transformation, low-grade glioma, MR imaging.

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Introduction

According to the National Cancer Registry, malignant tumours comprised about 156 000 new cases and 93 000 deaths in Poland in 2009. Primary brain tumours were the 11th most common cause of malignant tumour in males (2.1%; 1444 new cases in 2009) and the 15th most common in females (2.0%; 1362 new cases in 2009). Brain tumour mortality rate has remained stable since 1965 and according to the latest report, it was 2.8% (7.98/100 000) in males and 3.6% (7.48/100 000) in females [16]. Similar percentages of cases and deaths are reported in Europe and in the USA [11,26,35].

Gliomas comprising more than 40% of intracranial tumours constitute high-grade gliomas (HGGs) in 70-80% of cases [30]. Surgical excision with subsequent radio- and chemo-radiotherapy is the gold standard in treatment of HGGs. However, low-grade gliomas (LGGs) are mainly treated surgically and in some cases complimentary radiotherapy is administered. According to the 2011 diagnostic-therapeutic recommendations by the Polish Society of Clinical Oncology (PTOK), postoperative radiotherapy may be abandoned in the case of total surgical resection of oligodendroglioma, gemistocytic astrocytoma, if the tumour did not show contrast enhancement on preoperative (CT and MR) examination and if the patient was < 40 years of age. Postoperative chemotherapy may be considered in oligodendroglioma with 1p/19q loss of heterozygosity [3,21,36]. Gliomas WHO II which predominantly affect patients at the age of 30-40 are mostly characterised by diffuse infiltration of multiple cerebral structures [30]. Malignant transformation to a higher grade (WHO III and IV) in this group of tumours ranges between 35% and 89%. However, according to some reports, all gliomas WHO II undergo such transformation over time [37,48]. The median survival in patients with glioma WHO IV is < 2 years, whereas WHO II is 5-10 years. It is believed that the early detection of factors/parameters indicating anaplastic transformation may improve the prognosis [21,30,40].

Imaging studies are currently the standard method for early detection of changes in biology and malignancy of the tumour and precede the surgical procedure or stereotactic biopsy which is associated with an increased complication risk [21,27]. Malignancy is characterised by significant vascular proliferation within the tumour (neoangiogenesis)

[6,22,30,39,47]. According to the “angiogenic switch” theory, LGG progression to HGG must be accompanied by vascular proliferation within the tumour [22,47]. Neoangiogenesis results in increased relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV) and at a later stage contrast tumour enhancement on MR examination. Contrast enhancement as a marker of anaplastic transformation presents some disadvantages and poses some limitations. It appears late and its appearance proves that anaplastic transformation has already occurred. Additionally, it is a non-specific feature, resulting from the blood-brain barrier (BBB) breakdown due to e.g. inflammatory and ischaemic changes, radiotherapy as well as lack of the normal BBB in vasculature formed by neoangiogenesis. The extent of contrast enhancement also depends on the dose of glucocorticoids and even on the examination technique [5,17,35]. Although contrast enhancement is considered to be typical of HGGs, it should be remembered that about 40% of high-grade tumours do not show contrast enhancement whereas 10-39% of LGGs show contrast enhancement [21,28,30,35,37,45].

The aim of the study was to analyse MRI parameters indicating anaplastic transformation of gliomas WHO II.

Material and methods

Material

Forty-six consecutive patients were enrolled in the study (20 females and 26 males; range of age 36 ± 9 years) with supratentorial glioma WHO II. Patients were diagnosed in 2005-2011 at the Radiodiagnostic Department, Cancer Centre and Institute of Oncology in Gliwice, Poland. Surgical procedure/biopsy was performed at the Department of Neurosurgery, Medical University of Silesia, Sosnowiec, Poland. Multiparametric MR examination included morphological imaging, perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI) and proton magnetic resonance spectroscopy (¹H-MRS). Pathologic diagnosis was confirmed either by a surgical procedure or biopsy. In the majority of patients, i.e. (36/46) 78.3%, surgery was followed by excised area radiotherapy and/or radiotherapy for residual tumour 2 to 9 months after the diagnosis. The follow-up between the pathological diagnosis and the final follow-up MR examination was at least 18 months except for patients with earlier anaplastic transformation.

Methods

Magnetic resonance examinations were performed on a 1.5T (Magnetom Avanto, Siemens) or a 3.0T scanner (Achieva, Philips) with the standard head coil.

Conventional MR imaging

Conventional MR imaging consisted of morphological sequences of T1-weighted images before and after intravenous contrast agent application, T2-weighted images and fluid attenuated inversion recovery (FLAIR) images. Tumour volume was calculated based on T2-weighted images and FLAIR images, approximating to an ellipsoid.

Perfusion-weighted imaging

Perfusion-weighted imaging (PWI) was performed using dynamic susceptibility contrast perfusion magnetic resonance imaging (DSC MRI).

Scanner 1.5T: EPI SE (Echo Planar Imaging Spin Echo), TR/TE 1560/30 ms, Thk/gap 5.0/1.5 mm, matrix 128 × 128, FOV 250 × 250 mm, 50 data sets were acquired with a time resolution 1 per data set. TA was 1 min 26 s.

Scanner 3.0T: EPI GE (Echo Planar Imaging Gradient Echo), TR/TE 16(7°)/24(7°), Thk/gap 4.0/0.0 mm, matrix 64 × 128, FOV 230 × 230 mm. 50 data sets were acquired with a time resolution 1 per data set. TA was 1 min 29 s.

A gadolinium-based contrast agent was administered at the dose of 0.1 mmol/kg with the injection rate of 6 mL/s, followed by administration of 20 mL bolus of saline. Parametric maps of rCBV were calculated automatically by the software provided by the scanner producer. The region of interest (ROI) which was the basis for calculating rCBV drawn manually on each layer of the parametric map on which in the correlation with morphological images the tumour was detected. ROI was drawn in the solid tumour area ignoring cortical vessels, necrotic areas and treatment-induced changes. The value of rCBV in the tumour was normalised to normal appearing white matter in the contralateral hemisphere (normalised rCBV – nrCBV). The mean nrCBV was calculated and the max nrCBV was determined in the tumour.

Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) was performed using Echo Planar Imaging Spin Echo (EPI SE).

Scanner 1.5T: TR/TE 3100/99 ms, b = 0, 500, 1000 mm²/s, FOV 230 × 230 mm; matrix 192 × 192, Thk/gap 5.0/1.0 mm.

Scanner 3.0T: TR/TE 3080/70 ms, b = 0, 500, 1000 mm²/s, FOV 230 × 230, matrix 112 × 256, Thk/gap 4.0/1.0 mm.

Apparent Diffusion Coefficient (ADC) maps were calculated automatically using the software provided by the scanner producer. ROI was drawn manually on each layer of the parametric map in the solid tumour area in the correlation with morphological images. The mean ADC was calculated and the min ADC was determined in the tumour.

Proton MR spectroscopy

Point resolved localised spectroscopy (PRESS) was used for single-voxel spectroscopy (SVS) and chemical shift imaging multi voxel (CSI).

Scanner 1.5T: 3D CSI – TR/TE 2000/135 ms, SVS – TR/TE 1500/135 ms.

Scanner 3.0T: 3D CSI – TR/TE 2000-1500/144-288 ms, SVS – 2000-1500/144-288 ms.

Spectroscopy data were evaluated using Linear Combination of Model Spectra software (LCModel, version 6.1-4.F). Cho/Cr, Cho/NAA and NAA/Cr ratios (Choline, Cr – creatine, NAA – N-Acetylaspartic acid) were calculated. The voxel in SVS was placed in the solid tumour area. Spectroscopy data from every voxel placed in the solid tumour area were analysed in 3D CSI and in the subsequent analysis, the mean Cho/Cr, Cho/NAA, NAA/Cr were used.

Statistical analysis

Continuous parameters with normal distribution were presented as mean ± standard deviation (SD). Median and interquartile ranges were used to describe quantitative variables whose distribution differed from the standard. Significance of mean differences was tested with a *t*-Student test and an ANOVA proceeded by evaluation of normality and Levine's test. When significant effects were found, post hoc testing (NIR Fisher tests) of all possible comparisons was applied. Friedman's repeated measures ANOVA was used to test changes in not continuous values. Wilcoxon's test was used for post hoc analysis. To assess the differences between the variables, the Mann-Whitney *U* test was used to compare two independent groups. Statistically significant *p*-levels were assumed as < 0.05 (two-sided).

Statistical calculations and analyses were performed with STATISTICA (StatSoft) software version 9.0.

Results

Patients were divided into three groups depending on the course of disease (Fig. 1).

ST – stable group – total/subtotal tumour resection with no relapse/progression in clinical observation and follow-up MR examinations.

AT – anaplastic transformation group – pathologically verified tumour transformation to a higher grade of malignancy (WHO grade III or IV). Time to anaplastic transformation varied between 2 and 38 months. Transformation occurred within 12 months of the follow-up in 6/11 patients, between the 12th and the 24th month in 3/11 patients and after 24 months in 2 patients.

RP – radiological progression group – radiological progression without pathologically confirmed transformation.

Radiological progression was detected based on the increase in tumour volume by over 40% (1 patient in the RP group) or the occurrence of contrast enhancement with the normalised max nrCBV > 1.75 (11 patients in the AT group and 5 patients in the RP group) [17,23-26].

Initial pathologic diagnosis is presented in Table I.

The comparative analysis included 40 patients (29 from the ST group and 11 from the AT group). The selected parameters of PWI, DWI and ¹H-MRS were analysed prior to surgery/biopsy (initial MR), after surgery/biopsy (follow-up MR) and in the AT group in the final MR examination (final MR) where anaplastic transformation was detected prior to the surgical procedure and in the ST group in the final MR follow-up in which the tumour was stable at least 18 months after pathological diagnosis (final MR). Mean time of the follow-up MR in the AT group was 3 (1-8) months and in the ST group was 3 (1-8)

months. Mean time of the final MR in the AT group was 16 (3-38) months and in the ST group was 32 (18-66) months.

Subtotal tumour resection was achieved in the whole AT group, whereas in the ST group total tumour resection was achieved in 10/29 (34%) patients. The size of the residual tumour after surgery was statistically significantly higher in the AT group compared to the ST group (AT: 51.5 cm³ ± 37.7 vs. ST: 29.0 cm³ ± 37.9; *p* = 0.011).

Contrast enhancement on the initial MR was found in 15/40 (38%) tumours. Contrast enhancement in the AT group occurred in 5/11 (45%) tumours and in none of the patients, areas of contrast enhancement were resected during surgery/biopsy. However, the initial MR showed contrast enhancement in 10/29 (34%) patients in the ST group. The areas of contrast enhancement were totally resected in all patients, in 5/10 (50%) patients, total tumour resection was achieved and in 5/10 (50%), subtotal tumour resection was achieved in the area of contrast enhancement.

In the AT group on the initial MR in the area of contrast enhancement, mean nrCBV, mean Cho/Cr and mean Cho/NAA were significantly higher and the values of min ADC, mean ADC and NAA/Cr were

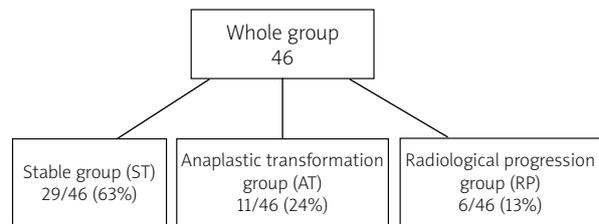


Fig. 1. Group division depending on the course of disease.

Table I. Initial pathologic diagnosis

Pathologic diagnosis	ST*	AT#	RP	Whole
Fibrillary astrocytoma WHO II	10/29 (34%)	6/11 (55%)	3/6 (50%)	19/46 (42%)
Gemistocytic astrocytoma WHO II	6/29 (21%)	4/11 (36%)	2/6 (33%)	12/46 (26%)
Oligodendroglioma WHO II	2/29 (7%)	0/11 (0%)	0/6 (0%)	2/46 (4%)
Oligoastrocytoma WHO II	11/29 (38%)	1/11 (9%)	1/6 (17%)	13/46 (28%)

ST – stable group, AT – anaplastic transformation group, RP – radiological progression group

* – 10/29 total surgical resection, # – 1/11 glioma transformed into glioblastoma and 10/11 gliomas transformed into anaplastic astrocytoma

Table II. Parameters of PWI, DWI, ¹H-MRS obtained in the contrast enhancement area and non-contrast enhancement area of the tumour, on the initial MR, in the stable group and the anaplastic transformation group

Parameters	ST* (n = 10/29)			AT** (n = 5/11)		
	CE	Non-CE	p	CE	Non-CE	p
Max nrCBV	2.67 (1.60-4.24)	1.44 (0.71-3.16)	0.005	3.15 (2.29-4.64)	1.47 (1.03-2.85)	0.079
Mean nrCBV	1.92 (1.39-3.67)	1.14 (0.63-2.69)	0.050	2.00 (1.68-3.19)	1.10 (0.77-1.78)	0.043
Mean Cho/Cr	1.60 (1.34-2.60)	1.44 (1.16-1.80)	0.007	1.85 (1.45-2.60)	1.59 (1.19-2.20)	0.043
Mean Cho/NAA	1.09 (0.55-3.81)	0.87 (0.49-1.80)	0.007	1.73 (1.42-2.26)	1.01 (0.80-1.79)	0.043
Mean NAA/Cr	1.36 (0.69-2.84)	1.65 (1.00-2.73)	NS	1.10 (0.82-1.51)	1.41 (0.89-2.79)	0.043
Min ADC [#]	1.24 (1.04-1.78)	1.32 (0.99-1.71)	NS	0.98 (0.70-1.14)	1.29 (0.81-1.43)	0.043
Mean ADC [#]	1.31 (1.13-1.86)	1.46 (1.13-1.79)	NS	1.20 (0.88-1.27)	1.38 (1.04-1.48)	0.043

ST – stable group, AT – anaplastic transformation group, CE – contrast enhancement area of the tumour, Non-CE – non-contrast enhancement area of the tumour

[#]ADC values *10⁻³ mm²/s, *On the initial MR in the ST group 10/29 (34%) tumours had CE area, **On the initial MR in the AT group, 5/11 (45%) tumours had CE area. The increase in max nrCBV > 1.75 preceded contrast enhancement up to 5-8 months in those tumours which did not enhance on the initial MR

Table III. Statistically significant differences between the stable group and the anaplastic transformation group on the initial MR, follow-up MR and final MR

Initial MR						
	max nrCBV	mean nrCBV				
AT	4.21 ± 0.67	2.48 ± 0.69				
ST	2.37 ± 0.69	1.47 ± 0.49				
p	0.001	0.001				
Follow-up MR						
	max nrCBV	mean nrCBV	min ADC	mean ADC		
AT	4.39 ± 1.09	2.56 ± 0.62	0.71 (0.59-1.02)	1.00 (0.70-1.21)		
ST	1.75 ± 0.81	1.13 ± 0.40	1.05 (0.79-1.59)	1.22 (1.1-1.71)		
p	0.001	0.001	0.001	0.006		
Final MR						
	max nrCBV	mean nrCBV	min ADC	mean ADC	mean Cho/Cr	mean Cho/NAA
AT	4.42 ± 1.83	2.93 ± 1.31	0.88 (0.75-1.31)	1.08 (0.87-1.44)	1.78 (1.34-3.17)	1.49 (0.78-2.09)
ST	1.68 ± 0.81	1.01 ± 0.44	1.09 (0.93-1.35)	1.22 (1.09-1.73)	1.30 (1.00-2.15)	0.84 (0.60-1.94)
p	0.001	0.001	0.020	0.049	0.030	0.030

AT – anaplastic transformation group, ST – stable group. In the ST group, max nrCBV and mean nrCBV values on the follow-up MR and final MR were significantly statistically lower compared to the results of the initial MR. Max nrCBV (2.37 ± 0.69 vs. 1.75 ± 0.81 vs. 1.68 ± 0.81; p = 0.042, p = 0.023). Mean nrCBV (1.47 ± 0.49 vs. 1.13 ± 0.4 vs. 1.01 ± 0.44; p = 0.030, p = 0.004).

In the AT group, on the follow-up MR, a statistically significant decrease in min ADC and mean ADC values in the remaining tumour area was observed compared to the initial MR examination. Min ADC (1.05 [0.71-1.36] vs. 0.71 [0.59-1.02]; p = 0.030). Mean ADC (1.29 [0.98-1.50] vs. 1.00 [0.70-1.21]; p = 0.030). Additionally, in the AT group an increase was observed in the value of Cho on the final MR compared to the initial MR examination. Cho/Cr (1.68 [1.10-2.19] vs. 1.78 [1.34-3.17]), Cho/NAA (1.32 [0.59-3.17] vs. 1.49 [0.78-2.09])

significantly lower compared to the non-enhancing area of the tumour (Table II).

Also in the ST group on the initial MR examination in the area of contrast enhancement, max nrCBV, mean nrCBV, mean Cho/Cr and mean Cho/NAA were significantly higher compared to the non-enhancing area of the tumour (Table II).

Compared to the ST group, tumours that underwent anaplastic transformation had statistically significantly higher values of mean nrCBV and max nrCBV on the initial MR examination, the follow-up and final MR examinations (Figs. 2 and 3, Table III). However, statistically significant differences between the groups in ADC values were observed on the fol-

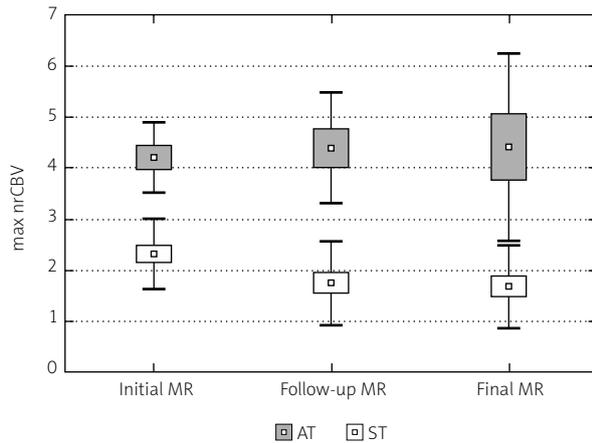


Fig. 2. Values of max nrCBV on the initial MR, follow-up MR and the final MR examinations in the stable group and the anaplastic transformation group.

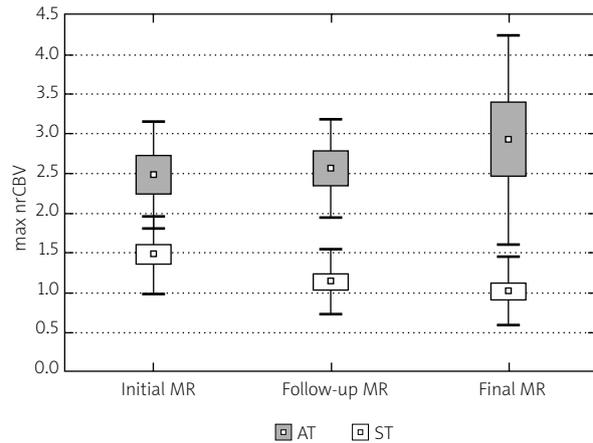


Fig. 3. Values of mean nrCBV on the initial MR, follow-up MR and the final MR examinations in the stable group and the anaplastic transformation group.

low-up and final MR whereas mean Cho/Cr and mean Cho/NAA were observed as late as on the final MR examination (Figs. 4A-H and 5A-J, Table III).

Discussion

Magnetic resonance imaging is a non-invasive method of evaluating certain features of the tumour assessed by pathological examination, for instance tissue microvascular density (MVD), cellularity, the presence of necrosis [4,5,12,15,32,34,38,50]. Malignancy is characterised by vascular proliferation within the tumour (neoangiogenesis) [6,22,30,39,47]. According to the “angiogenic switch” theory, the essence of LGG anaplastic transformation is vascular proliferation in a previously avascular tumour [22,47]. Vessels formed by neoangiogenesis differ in their structure from normal vasculature (tortuosity, lack of maturity and increased permeability). On standard MR imaging, neoangiogenesis manifests as the area of contrast enhancement. Contrast enhancement as a marker of anaplastic transformation appears late and its appearance proves that anaplastic transformation has already occurred. However, PWI gives access to information on the capillary microcirculation of tissues and reflects tissue MVD by measuring rCBV, prior to the occurrence of contrast enhancement [5,35]. Dancaivijitr *et al.* confirmed that in the group of gliomas which underwent anaplastic transformation, continuous rCBV growth (within 12-18 months) preceded the occurrence of an abnormal

area of contrast enhancement in the tumour [13]. Law *et al.* suggested the cut-off value for the normalised to the normal appearing white matter rCBV > 1.75 on MR examination prior to surgery as the feature differentiating rapidly progressive LGGs (median 8 vs. 154 months) [24,26]. The similar correlation was confirmed by Caseiras *et al.* using the same cut-off value for rCBV – “the median time to progression among subjects with rCBV > 1.75 was 365 days, while there was 95% confidence that the median time to progression was at least 889 days among subjects with rCBV < 1.75 ” [7]. Referring to the findings of Law *et al.*, Al-Okaili *et al.* used the same cut-off value for rCBV characterising the area of the increased perfusion in the study on differential diagnosis of intra-axial brain masses. Gliomas with rCBV > 1.75 corresponded to HGGs with sensitivity of 88%, specificity of 100%, PPV of 100%, NPV of 67%, compared to LGGs [1]. Although the normalised rCBV = 1.75 is the most frequently accepted cut-off value differentiating LGGs from HGGs as well as LGGs with short and long transformation time, other clearly distinct values are also reported. In the study by Arvin-da *et al.*, the cut-off point for nrCBV mostly differentiating LGGs from HGGs was 2.93, whereas Morita *et al.* obtained nrCBV = 0.94 [2,33]. In our material in the AT group, the increase in max nrCBV > 1.75 preceded contrast enhancement in the same tumour area within 5-8 months in 6/11 (45%) patients. In the remaining 5/11 (55%) patients, max nrCBV > 1.75 was found in the area of contrast enhancement from

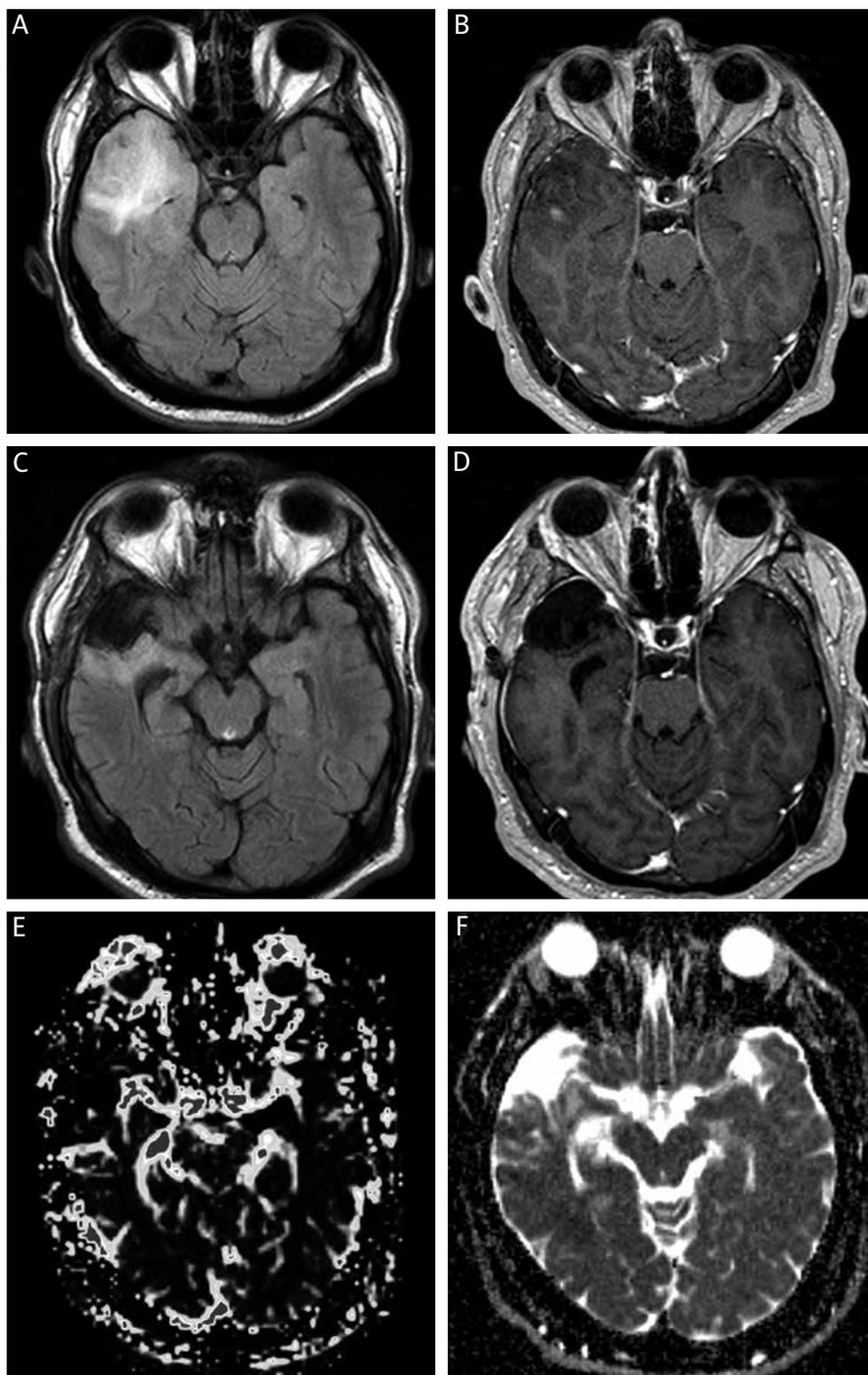


Fig. 4. A–F) Fibrillary astrocytoma WHO II out of the stable group, the initial MR: FLAIR (A) and T1-weighted image after intravenous contrast agent application (B), the final MR: FLAIR (C) and T1-weighted image after intravenous contrast agent application (D), PWI – rCBV map (E), DWI – ADC map (F).

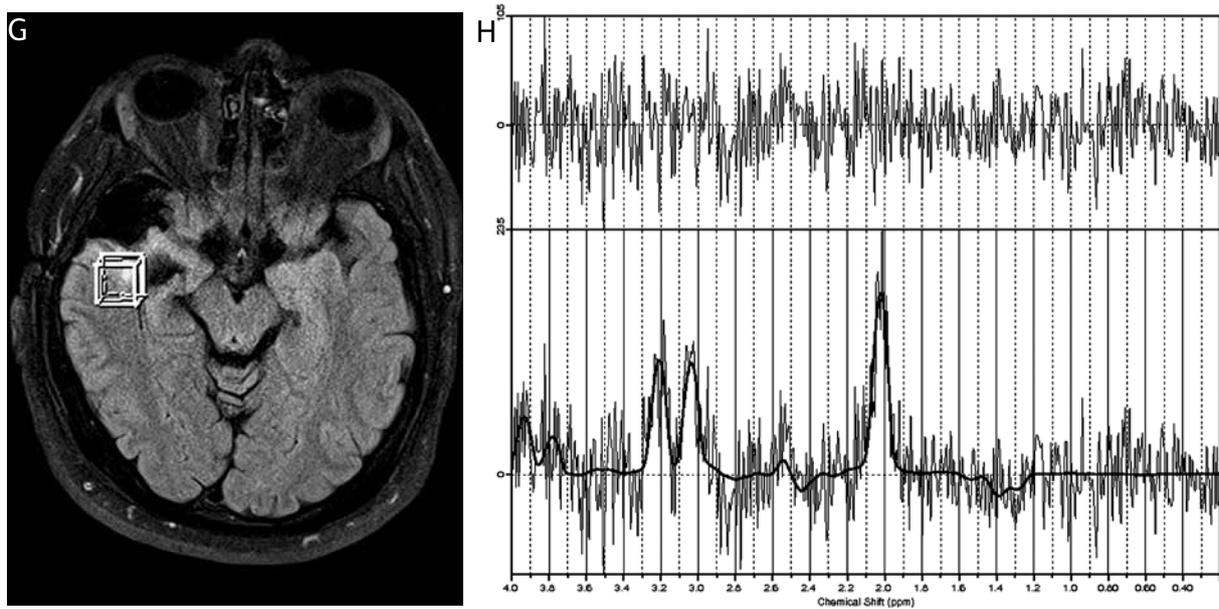


Fig. 4. G–H) Fibrillary astrocytoma WHO II out of the stable group, the initial MR: $^1\text{H-MRS}$.

the very beginning. Moreover, max nrCBV and mean nrCBV in AT group were significantly higher on the initial MR, follow-up MR and the final MR examinations compared to the ST group. In the ST group max nrCBV and mean nrCBV were significantly lower on the follow-up MR and the final MR examinations compared to the initial MR examination, which may have been due to resection of contrast enhancement area characterised by significantly increased nrCBV in relation to the remaining tumour area.

In our material, the extent of tumour resection in the ST group was significantly higher compared to the AT group. The extent of tumour resection significantly influenced progression-free survival (PFS) and overall survival (OS) in LGG patients, which is consistent with the reports of other researchers [19,31,43]. Our observations confirm that next to the extent of resection, excision of contrast enhancement area is essential for further course of disease. In our material, none of the patients from the AT group had contrast enhancement area resected whereas in the ST group contrast enhancement area was resected in all patients. In both groups in the area of contrast enhancement nrCBV and Cho/Cr and Cho/NAA ratios were significantly higher compared to the non-enhanced tumour area, which indicates higher potential malignancy of this part of tumour. Additionally, in the AT group in the area of contrast enhancement

ADC was significantly lower compared to the outside of this area. Chaichan *et al.* confirmed that in patients with LGGs enhanced after contrast agent administration, the 5-year OS, PFS and malignant transformation-free survival were shorter compared to patients with non-enhancing LGGs (70 vs. 85% [$p = 0.002$], 32 vs. 49% [$p = 0.008$] and 74 vs. 90% [$p = 0.002$], respectively). Moreover, the only factors that were consistently shown to be associated with tumour recurrence or malignant degeneration are preoperative contrast enhancement, tumour size, and subtotal resection. Additionally, in the multifactorial analysis, Chaichan *et al.* confirmed that LGG contrast enhancement is an independent factor determining decreased survival ($p = 0.006$), increased recurrence ($p = 0.04$) and the trend towards a higher incidence of malignant degeneration ($p = 0.15$). However, Chaichan *et al.* did not analyse parameters of PWI, DWI, proton MR spectroscopy ($^1\text{H-MRS}$) [9,10]. The criteria for Response Assessment in Neuro-Oncology (RANO) regarding the assessment of response to treatment of non-enhancing LGGs indicate that the area of contrast enhancement in the tumour corresponds to malignant transformation although it is a non-specific feature [45], and parameters of PWI, DWI, $^1\text{H-MRS}$, PET though mentioned in the model protocol are not included in the treatment-response assessment. According to the authors of the RANO

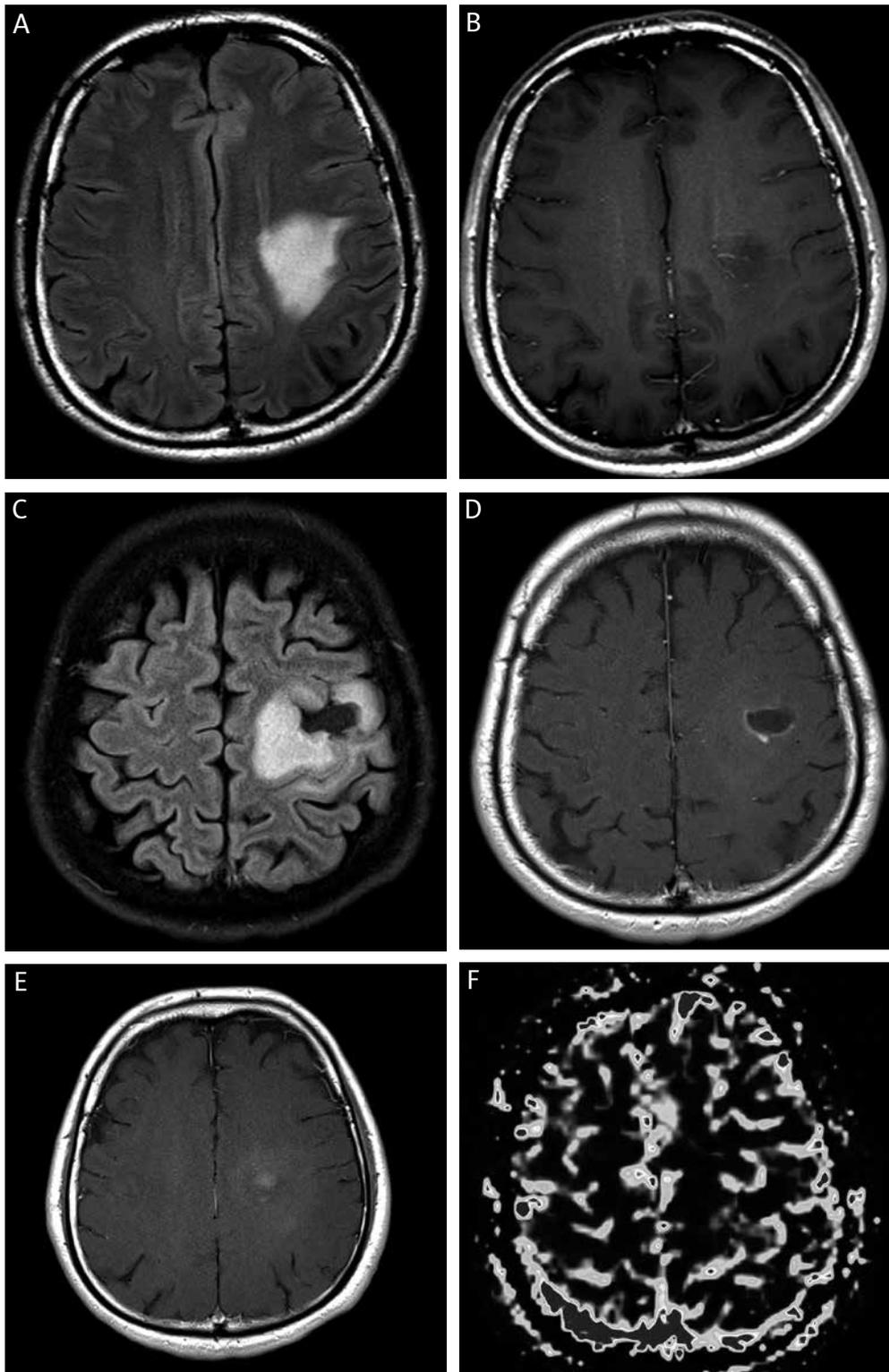


Fig. 5. A–F) Fibrillary astrocytoma WHO II out of the anaplastic transformation group, the initial MR: FLAIR (A) and T1-weighted image after intravenous contrast agent application (B), the final MR: FLAIR (C) and T1-weighted image after intravenous contrast agent application (D, E), PWI – rCBV map (F, G).

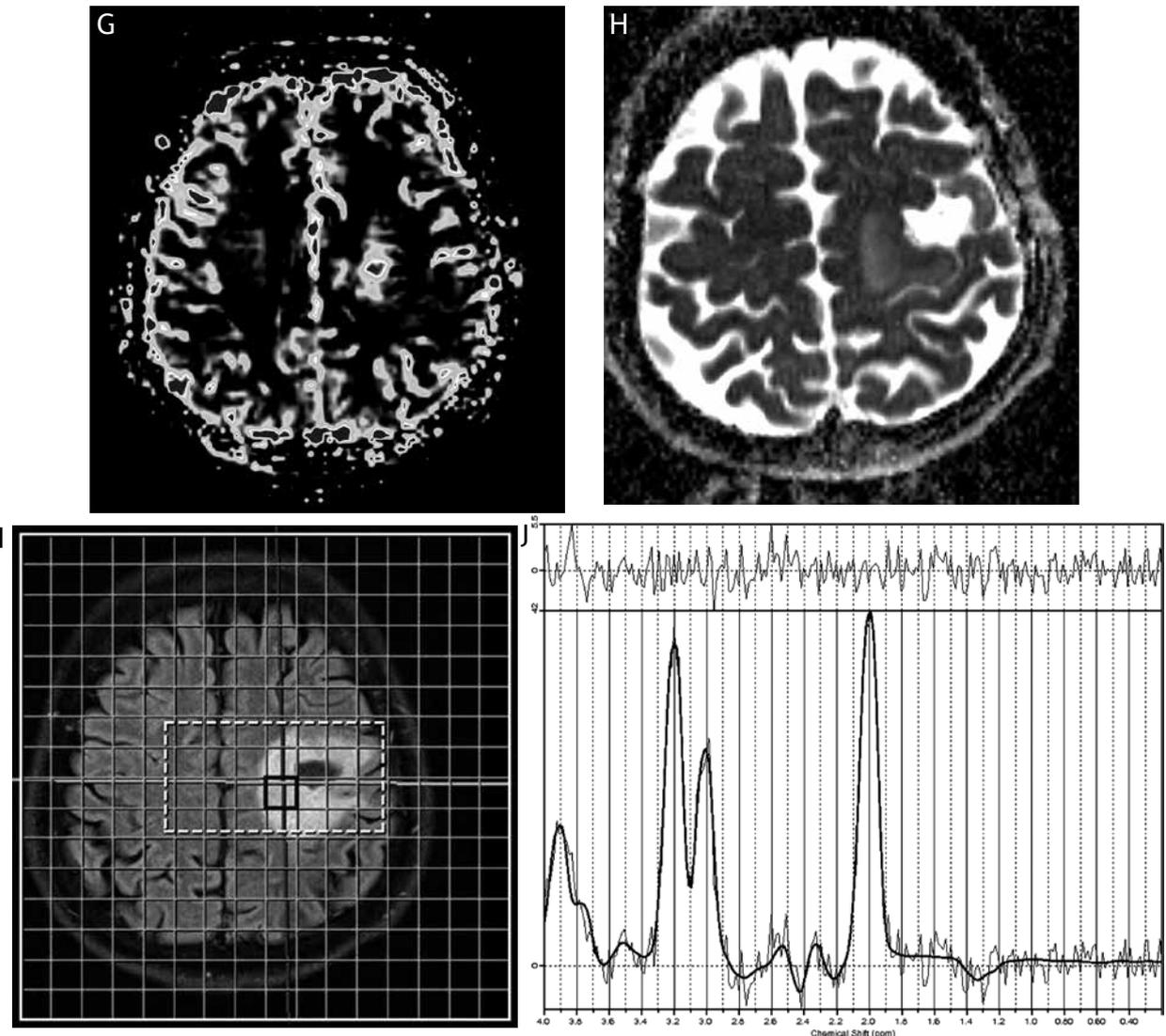


Fig. 5. G–J) Fibrillary astrocytoma WHO II out of the anaplastic transformation group, the initial MR: PWI – rCBV map (**F, G**), DWI – ADC map (**H**), ^1H -MRS (**I, J**).

criteria, the percentage of gliomas WHO II enhancing after contrast agent administration is reported to be at the level of 10% and mainly in the oligodendroglioma subgroup. The post-treatment occurrence of a new area of contrast enhancement in gliomas WHO II is first interpreted as malignant transformation [45]. According to RANO, “for progression, two types of MRI progression have to be distinguished and reported separately: the development of or an increase in enhancement suggestive of malignant transformation, and linear progression of a still non-enhancing lesion”.

In our study, astrocytomas and oligoastrocytomas occurred in both groups (ST and AT) whereas oligo-

dendrogliomas exclusively in the ST group. A gemistocytic component was found more frequently in the AT group (36% of tumours) compared to the ST group (21% of tumours).

In the multifactorial analysis regarding early prognostic factors related to progression and malignant transformation of LGGs, Joung *et al.* confirmed that apart from total tumour resection, a gemistocytic component in LGGs was related to shorter PFS and independently influenced the occurrence of malignant transformation [19]. Additionally, in trials regarding LGG treatment with radiotherapy, the median survival of > 5 years was reported for patients with oligodendroglioma compared to other

gliomas WHO II for which the median survival was < 5 years [20,42,44].

There are no explicit reports on the ADC cut-off value differentiating gliomas depending on the tumour grade [2,8,41,46]. However, it is generally accepted that the higher the tumour grade, the lower ADC values [46]. Server *et al.* and Arvinda *et al.* suggested the minimum ADC = 1.07×10^{-3} mm²/s and the mean ADC = 0.985×10^{-3} mm²/s as the ADC cut-off values differentiating HGGs from LGGs [2,41]. However, Catalaa *et al.* noted that HGGs and LGGs did not differ in ADC values [8]. In our material, min ADC and mean ADC did not differ significantly between AT and ST groups on the initial MR examination. However, min ADC and mean ADC were significantly lower in the AT group on the follow-up MR and the final MR examinations compared to the ST group. In the AT group the follow-up MR revealed a statistically significant decrease in min ADC and mean ADC values in the remaining tumour area compared to the initial MR examination. It may be related to the increased component of post-treatment ischaemic changes or gliosis. It cannot be clearly determined which process or component mainly contributed to the decrease in the ADC value.

The cut-off value for Cho/Cr and Cho/NAA reported by various researchers differentiating LGGs from HGGs is wide (1.35 to 2.04 for Cho/Cr and 1.60 to 2.49 for Cho/NAA) [14,23,29,41,49]. Hlaiheli *et al.* confirmed that in the group of oligodendrogliomas WHO II which underwent anaplastic transformation, mean Cho/Cr ratio above 2.4 was the earliest marker of the transformation with a mean delay of 15.4 months. Whereas normalised rCBV elevation > 2 occurred an average of 8 months before the malignant transformation. Authors suggested that “the increase in cell membrane production and cell density, as attested by the elevation of the choline/creatine ratio, may generate an ischaemic process that initiates vascular proliferation in the infiltrative tissue” [18]. In our study, in the AT group mean Cho/Cr and mean Cho/NAA were significantly higher as late as on the final MR examination compared to the ST group. The increase in Cho over time was observed in the AT group, i.e. mean Cho/Cr and mean Cho/NAA were higher on the final MR examination compared to the initial MR examination. Our analysis comprised of ¹H-MRS with a long TE: 135-288 ms, whereas Hlaiheli *et al.* analysed mainly single-voxel short TE: 32 ms ¹H-MRS. Moreover, in our material there were different gliomas WHO II

(fibrillary astrocytoma, gemistocytic astrocytoma, oligodendroglioma, oligoastrocytoma), whereas Hlaiheli *et al.* analysed only oligodendrogliomas. We had longer follow-up and more gliomas which underwent anaplastic transformation.

Conclusions

Multiparametric MR examination allows the detection of LGGs with high probability of rapid anaplastic transformation and the detection of transformation prior to the occurrence of contrast enhancement. The value of nrCBV is the most useful in the diagnosis of anaplastic transformation. The resection of contrast enhancement area of the tumour significantly increases time to anaplastic transformation of LGGs.

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