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NAPREDNE TEHNIKE MAGNETNE REZONANCIJE U RANOM RAZDVAJANJU PSEUDO-PROGRESIJE OD PROGRESIJE KOD PACIJENATA SA GLIOBLASTOMOM MULTIFORME

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Advanced magnetic resonance techniques in early differentiation of pseudo-progression vs. progression in patients with Glioblastoma multiforme

Napredne tehnike magnetne rezonancije u ranom razdvajanju pseudo-progresije od progresiju kod pacijenata sa glioblastomom multiforme

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Pseudo-progression vs. progression in GBM
Advanced MR techniques in early differentiation of pseudo-progression vs. progression in patients with glioblastoma multiforme

Abstract

Introduction. The diagnosis of glioblastoma multiforme progression may be confounded by a phenomena termed pseudoprogression (PSP) and pseudoresponse (RCT) which has become more common with the adoption of radiation therapy with concurrent and adjuvant application of Temozolomide (CRT). Distinguishing of these phenomena is based on follow-up scans since no single imaging method or technique is yet capable to perform their discrimination. In this study we evaluated dynamic susceptibility contrast (DSC perfusion) imaging and magnetic resonance spectroscopy to predict the prognosis and time to progression in patients with glioblastoma multiforme. Methods. Forty patients with primary glioblastoma multiforme were included in the analysis. Patients were examined in 3rd week after surgery and 10th week after the beginning of CRT. Magnetic resonance exams were performed using 1.5 T MR scanner (Avanto; Siemens, Erlangen, Germany). The maps of perfusion parameters and time-to-peak (TTP) parameter were calculated using DPTools v3.79 software. 3D CSI PRESS magnetic resonance spectroscopy was performed in area corresponding to contrast enhancement on T1W images. Results. 32 of the 40 patients had progressive disease and 8 to have pseudo-progression. Progressive disease show mean time to peak values of 33±7 s on the 3th and 30±5 s in 10th week with no statistical significance between these two periods, p>0.05. Patients with pseudo-progression show mean time to peak values of 32±8 s on the 3th week and 43±9 s on the 10th week and it was statistically significant difference p<0.05 which favors better response to therapy. Spectroscopy results show presence of Glycine peak at 3.56 ppm in 6 patients with progressive disease which was not seen on spectra with pseudo-progression. Conclusion. The observed significant differences in TTP values for PSP and RCT can provide basis for distinguishing two entities. The presence of glycine peak in MR spectra could be marker of RCT.

Key words: glioblastoma multiforme, pseudo-progression, MR spectroscopy, MR Perfusion
Apstrakt

Uvod/Cilj Uvođenje tretmana glioblastoma zračnom terapijom uz konkurentnu i adjuvantnu primenu Temozolomida (CRT) dovelo je do pojave nove dijagnostičke dileme – potrebe za razlikovanjem pseudo-progresije i presudo-odgovora. Razlikovanje ova dva fenomena za sada je moguće samo evaluacijom MRI snimaka u više vremenskih tačaka u toku terapije, dok nove tehnike koje bi pomogle u njihovom razlikovanju nisu još uvedene. U radu je analizirana mogućnost primene time-to-peak mapa dinamičkog perfuzionog imidžinga i magnetno rezonantne spektroskopije u utvrđivanju odgovora tumora na terapiju. Metode Analizirano je 40 pacijenata sa primarnim glioblastomom multiforme. Pacijenti su snimani u 3. nedelji nakon operacije i 10. nedelji od početka CRT. Pregledi na aparatu za magnetnu rezonanciju rađeni na aparatu 1.5 T Avanto Siemens, Erlangen Nemačka. Mape perfuzionih parametara su generisane i analizirane korišćenjem programa DPtools v3.79. 3D CSI PRESS spektroskopija sa dugim i kratkim vremenom eha je rađena kod svih pacijenata. Rezultati Kod 32 od 40 pacijenata je dijagnostikovana progresija bolesti, a kod 8 pacijenata je dijagnostikovana pseudo-progresija. Kod pacijenata sa progresijom bolesti dobijene time-to-peak vrednosti su 33±7 s u 3. nedelji i 30±5 s u 10. nedelji, što ne predstavlja statistički značajnu razliku. Vrednosti ovog parametra za pseudo-progresiju su 32±8 s u 3. nedelji i 43±9 s u 10. i statistički značajno se razlikuju (p<0.05). Rezultati spektroskopije ukazuju na prisustvo glicinskog pika kod 6 pacijenata sa progresijom bolesti dok kod pseudo-progresije ovaj metabolit nije bio prisutan. Zaključak Analizirane magnetno rezonantne tehnike su pokazale veoma uspešnu primenu u postavljanju dijagnoze progresije bolesti tokom terapije kod pacijenata sa glioblastomom.

Ključne reči: glioblastom multiforme, pseudo-progresija, MR spektroskopija, MR perfuzija
Introduction

Glioblastoma multiforme (GBM) is the most common brain tumor characterized by high aggressiveness and poor outcome. The current standard of treatment is surgical resection, followed by concomitant chemotherapy (CM) and radiotherapy (RT) [1,2]. The evaluation of GBM response to therapy is governed by several criteria which consider findings in post-treatment radiological and clinical evaluation. According to Macdonald criterion [3], the tumor recurrence (RCT) can be established by presence of 25% increase in the post-contrast T1W magnetic resonance (MR) images and clinical deterioration. Recently adopted RANO (Response Assessment in Neuro-Oncology) [4] criterion states that, within period of 12 weeks upon completion of RT, true progression can only be established if majority of the new post-contrast enhancement in T1W images appears in region outside the area treated by the RT. However, the introduction of the new first-line chemotherapeutic temozolomide (TMZ) led to observation of a relatively new phenomenon in follow-up of GBM treatment – pseudoprogression. Pseudoprogression (PSP) is a phenomenon of subacute changes observed in glioma imaging, subsequent to radiochemotherapy, suggestive of progression, with or without associated clinical sequelae, which resolve spontaneously without further therapy [5]. In contrast to radiation necrosis which appears months to several years after RT [6], PSP usually can be observed several weeks after RT [7]. Beside the similar appearance of PSP and RCT on post-contrast T1W images, the first could be also followed by clinical deterioration. The correct distinguishing of PSP and RCT has a large impact on decision whether TMZ application should be continued or ceased and changed with an agent specific for recurrent tumor (e.g. Avastin etc.).

The advanced MRI methods, such as diffusion weighted imaging (DWI), perfusion imaging and magnetic resonance spectroscopy (MRS) showed variable success in distinguishing two entities. The principal obstacle in evaluation of GBM response to therapy using DWI lies in the inherently high heterogeneity of tumors appearance on DWI and maps of the apparent diffusion coefficient (ADC), a feature which is often further increased by treatment. Chu et al [8] had reported that DWI obtained at very high \( b \)-values (3000 s-mm\(^{-2}\)), hardly obtainable in clinical MRI setups, can be used in distinguishing PS and RCT.
Since neoangiogenesis and increased vascular density are prominent features of recurrent tumors, the techniques which enable their tracing have a large potential in differentiation of RCT from radiation necrosis. So far, there is a single report dealing with the use of dynamic contrast enhanced (DCE) imaging in distinguishing RCT from PSP. Suh et al used ratios of areas under initial and, somewhat arbitrarily, selected final part of DCE curve to successfully distinguish these entities [9].

Perfusion parameters derived from the dynamic susceptibility weighted imaging (DSC) such as relative cerebral blood flow (rCBF), mean transition time (MTT) and particularly relative cerebral blood volume (rCBV) have been successfully used to distinguish residual/recurrent neoplasm from treatment-related radiation necrosis [10,11]. Few studies have reported the use of the DSC parameters in differentiation of RCT and PSP, although with variable success. Song et al [12] reported that mean rCBV cannot be used for differentiation of RCT and PSP. Kong et al [13] reported that PSP showed significantly lower rCBV values compared with RCT so they could be distinguished with cut-off value 1.45 (81.5 % sensitivity, 77.8 % specificity). There are reports that PSP and RCT can be distinguished with somewhat higher sensitivity and specificity when cut-off value 1.8 for rCBV is used [5,14]. Mangla et al [15] evaluated rCBV values in patients with GBM before and 1 month after RT-TMZ treatment and observed 41% decrease in rCBV in the PSP patients, in contrast to 12% increase in rCBV for the RCT patients. However, the studies dealing with classical analysis of perfusion maps suffer from several limitations. First, different modalities were used for correction of contrast leakage which is usually achieved by use of pre-bolus application of small dose of contrast agent or by use of software; in some studies this correction was not used et al [14]. Second, regions of observed increase of rCBV values may contain tissue which responded to treatment as well as viable tumor in different fractions — even a minute presence of GBM (abundant less than 5 % in total) is considered as RCT [16]. There are several studies involving detailed analysis of rCBV maps in tumor region. Baek et al [17] used histogram analysis of perfusion maps in two time points after completion of RT and CM and found that percent change in histogram parameters can be used for distinguishing PSP and RCT. Cha et al [18] implemented complex approach by combining histograms of ADC and rCBV maps and traced changes in their parameters between two follow-up time points. They found that difference histograms with high sensitivity and accuracy can be used for distinguishing RCT and PSP.
Tsien et al [19] used the voxel-based analysis of rCBV maps before and after received therapy and significantly lower values of this parameter in PSP when compared to RCT patients. Hu et al [16] had used interesting approach for differentiation of PSP and RCT as well as for obtaining tumor burden in enhancing lesion. In their study a combination of histological analysis of tumor tissue and evaluation of perfusion maps was used in obtaining rCBV cut-off values which resulted in complete differentiation of PSP from RCT.

Time-to-peak (TTP) parameter can be determined by measuring interval from contrast agent administration to appearance of minimum in time course of DSC signal change. Maps of this parameter are usually generated automatically using standard software packages built in MRI console. However, due to variation between time of contrast injection and the arrival of the bolus in the cerebral arteries the comparison of absolute TTP values is difficult to compare. Therefore, in order to enable comparisons between TTP for different individuals or examinations, standardized TTP maps should be used [20]. This parameter was extensively used in computerized tomography (CT) for differentiation of pathologies outside of CNS and in, characterization of strokes, and in differentiation of GBM from solitary metastasis. However, to our knowledge, TTP derived from DSC images has been used only for evaluation of the stroke-affected tissue [21], but not for assessment of tumor response to therapy.

Magnetic resonance spectroscopy (MRS) is frequently applied as a tool for differentiation various brain pathologies. However, the discrimination power of MRS in follow-up of tumor response to therapy is limited by considerable overlapping of spectroscopic profiles of RCT and radiation/chemo therapy. This is particularly pronounced in differentiation of RCT and TMZ/RT treatment-induced PSP since both could have the same spectroscopic features including reduction of N-acetyl aspartate (NAA), elevation of choline (Cho) and large increase in lactate/lipid concentrations [22,23].

Several studies showed that GBM cells release excitotoxic levels of in extracellular space [24,25]. This may lead to increased levels of this excitatory neurotransmitter which is followed by elevation of levels of inhibitory transmitters particularly Glycine (Gly). Although there is a number of biochemical studies which dealt with transport and accumulation of glycine in GBM cells, the reasons for this remain unclear [26]. Increased
levels of Gly were also observed in some metabolic diseases, meduloblastoma and in the low grade tumor central neurocytoma.

In this study we evaluated possibility of TTP application, as minimally subjective parameter, in distinguishing of PSP from RCT. Sensitivity and specificity of differentiation were compared to that of the routinely reported DSC parameter rCBV. The level of glycine, obtained from analysis of MR spectra of tumor tissue, was tested as marker for establishing presence of PSP.

**Methods**

**Patients**

This study included 40 patients with primary GBM, confirmed by histopathological analysis, (27 males and 13 females, mean age 51 years) who underwent surgical resection followed by concomitant TMZ and RT. Treatment protocol included RT plus continuous daily TMZ (75 mg/m²/day) followed by 6 cycles of adjuvant TMZ (150 mg/m² for 5 days every 28 days). The treatment started one week after the surgery.

**MRI examination**

All MRI examinations were performed using 1.5T MR scanner (Avanto; Siemens, Erlangen, Germany) in the 3rd and 10th week upon the surgery (2nd and 9th week after start of CMT+RT therapy). The first part of protocol included T1W (TR/TE 550/9.4 ms), T2W (TR/TE 3808/89ms) and FLAIR imaging (TR/TE/TI 9900/126/2500). The MR examinations were repeated in the in the 6th month after surgery in order to establish definitive diagnosis of PSP and RCT: decrease of postcontrast enhancement on T1w images was indicative to presence of PSP, otherwise RCT was diagnosed. The obtained images were reviewed by neuroradiologist with 18 years of experience.

**DSC**

DSC MR imaging was performed using a dynamic T2*-weighted echo-planar MR sequence. Multisection image data were acquired for a total of 90 s, with the bolus contrast injection occurring after 13 seconds to get a sufficient number of baseline images. The images were acquired in the axial plane with mid-slice position at the level of the basal ganglia. A contrast medium bolus (dose, 0.1 mmol/kg Gadovist, Bayer Schering Pharma, Berlin, Germany) was administered using an MRI injector (Ulrich Medical; Mississippi™ (MRI), Germany) with a 5 mL/s flow rate.
The data from the DSC MR images were transferred to a PC workstation and analyzed using software package DPTools (Version 3.79). Time courses of DSC signal were obtained from four ROIs (20-30 pixels in size) placed in regions of the row DSC images corresponding to contrast enhancement in T1W images. Arterial input function was selected by placing single ROI over the middle cerebral artery located in the hemisphere contralateral to lesion. After obtaining of rCBV maps, four ROIs (20-30 pixels) were placed within regions of the map which correspond to contrast enhancement in T1W images or perifocally to surgical cavity if no post-contrast enhancement was observed. The manner described above. rCBV associated with the each positioned ROI were obtained and normalized (nCBV) by division by rCBV obtained for contralateral white matter. DSC curves were obtained from ROIs identically positioned as previously described and averaged. TTP parameter was determined as time period from the application of contrast agent to appearance of minimum of curve.

\textit{1H MRS}

1H MRS was performed using 3D CSI PRESS with long echo time (TE=135 ms). Voxel matrices were placed in the area of the high signal intensities on T2W/FLAIR images which corresponded to edema and contrast enhancement on T1W. The spectra evaluation was performed using commercial Syngo v15 workstation (Siemens, Erlangen, Germany) Metabolites as Cho, Cr, N-acetylaspartate (NAA) and a single peak at 3.56 ppm in long echo time defined as Gly were taken into account. The area under the curve of a metabolite Cho, NAA was considered as relative concentration and was measured in terms of ratios in relation to Cr (Cho/Cr, NAA/Cr).

\textit{Statistical analysis}

Statistical calculation was performed in IBM SPSS Statistics17. Comparisons between obtained mean TTP values between patient with pseudo-progression and true progression were performed using ANOVA with Bonferroni correction. Statistical significance was set at \( p=0.05 \)

\textit{Results}

In the 3\textsuperscript{rd} week from the beginning of concomitant RT and CMT areas of high signal were observed in FLAIR images in both patients with PSP and RCT. However, no post-contrast enhancement was detected in T1W images.
In the 10th week from start of therapy MR imaging examinations demonstrated a new enhancement in post-contrast T1W images patients in both patients with PSP and RCT (figure 1 b and 1d). In addition hyperintensities were observed in the regions of FLAIR images that correspond to the non-enhancing portion of the lesion in both entities (figure 1a and 1c). The follow-up MR imaging in the sixth month upon surgery revealed presence of RCT in 32 patients (80%), while the PSP was established in 8 (20 %).

Figure 2 shows box-whiskers plot of nCBV values for PSP and RCT in the 3rd and 10th week after surgery. No significant differences were found between nCBV values in pseudo-progression in the 3rd week (mean 2.94±0.95) and in the 10th week (mean 3.31±1.32) after tumor resection. Also, no significant differences were found between nCBV values for progressive disease in the 3rd week (mean 2.99±0.97) and in the 10th week (mean 3.30±1.05). Similarly, no differences were found between PSP and RCT when nCBF values were analyzed (3rd week after surgery: nCBF(PSP)=2.62±1.10, nCBF(RCT)=2.80±1.41; 10th week: nCBF(PSP)=2.36±1.24, nCBF(RCT)=2.74±1.2).

The mean DSC curves for RCT and PSP in the 3rd week and in 10th week after surgery are shown in Figures 3a and 3b.

Figure 4a shows box-whiskers plot of TTP values for PSP and RCT in the 10th week after surgical resection. No significant differences (p>0.05) were found between TTP values in the first (mean 30 ± 5 s) and in the second time point (33 ± 7 s) in RCT group. Significant difference (p<0.05) was observed when the TTP values for PSP were compared: 32 ± 8 s in 3rd week and 43 ± 9 s on the 10th week (Figure 4a). Also, TTP values for RCT and PSP differed significantly in the 10th week, but not in the 3rd after surgery.

The receiver operating characteristic (ROC) curves for differentiation RCT from PSP for the 3rd week and the 10th week after surgery are shown in Figures 5a and 5b. It can be noticed that differentiation of PSP and RCT, based on TTP values observed in the 3rd week after surgery, is characterized by intermediate sensitivity and high specificity (64 % and 94 % respectively). However, in the 10th week specificity and sensitivity for their differentiation were 78% and 99% (AUC=0.86, p<0.001), respectively.

In 1H MR spectra for all 40 patients we observed markedly decreased NAA/Cr ratios and prominently elevated Cho/Cr ratio (Cho/Cr > 2) compared to contralateral normal-appearing brain tissue (Cho/Cr= 0.8-1). The inverted lactate peak could be identified in most of the cases and usually was high in the cystic/necrotic portion of the tumor. Presence
of Gly peak at 3.56 ppm was established in spectra of enhancing lesion in 6 (18%) patients with progressive disease (Figure 6b) but not in spectra of pseudo-progression (Fig. 6a). The Gly was detected only in solid part of the tumor with Gly/Cr ratio in range from 0.50 to 0.95. The observed ratio of Gly/Cho was low and range from 0.12 to 0.18.

Discussion
In this study we used modified (“in-house”) protocol for MRI assessment of tumor response to combined RT and CMT – the first follow-up MRI was performed in course of therapy (3rd week after surgery) while the second was performed in the first week after its finalization. The commonly reported protocols employ baseline MRI performed within 48 h after surgery and the second time point is usually within 4-12 weeks after completion of therapy. We found no significant differences between nCBV values for PSP and RCT regardless of time point used for comparison. The nCBV values obtained early in the course of therapy (3rd week after surgery) are in agreement with values previously reported for non-treated GBM which suggest that no changes in this parameter can be observed at this time point. The finding that nCBV cannot differentiate PSP and RCT in the 10th week after surgery disagrees with findings of the majority studies which evaluated the use nCBV in assessment of GBM response to therapy [5,13,14]. However, in those studies there are differences in cut-off values and performance of nCBV in differentiation between PSP and RCT. Song et al [12] and Sugahara et al [27] reported that this parameter has no value in solving this diagnostic dilemma. Leimgruber [28] even claims that nCBV cannot distinguish between RCT and effects of therapy. The absence of concordance between findings of those studies may be attributed to several causes. First, the vasodilatation and inflammation which induced by application of concomitant therapy could lead to overlap in nCBV values for PSP and RCT. Further, different algorithms for estimation of perfusion parameters, subjectivity in AIF selection, presence/absence of contrast leakage correction may introduce errors in nCBV determination. For example, using blood pool constrained agent and standard gadolinium based agent, Gahramanov [29] demonstrated that absence of correction to leakage of contrast agent may lead to 20 % increase in false negative RCTs. Last but not least, the choice of ROI positioning may be determining because suspected RCT/PSP may contain portions of tissue that responded to therapy as well as viable tumor
Albeit, the procedures involving advanced analysis of perfusion parameters showed good performance in distinguishing PSP and RCT [17–19], the complexity of their algorithm makes them hardly suitable for routine clinical assessment of GBM response to treatment.

When evaluating performance of TTP we found that this parameter, measured in the first week after therapy, could be used in distinguishing RCT and PSP with relatively high specificity and sensitivity. The prolonged TTP in PSP compared to RCT may be explained by presence inflammation and radiation induced damage of blood vessels and consequent decrease of tissue perfusion. This is partly supported by lower values (but not significantly) of nCBF in PSP compared with RCT found in this study. In addition therapy-induced damage of vessels may result in leakage of contrast agent in interstitium which may lead to increase of TTP value. However, permeability data which would confirm our assumption are available for de novo/recurrent GBM and normal tissue, but not for pseudo-progression [30,31]. The use of TTP has some advantages over standard perfusion parameters in evaluation of GBM response to therapy. The values of rCBV and rCBF highly depend on choice of Arterial Input Function (AIF) which in turn relies on operator’s experience [21,32]. Further, local AIF usually doesn’t match that from large arterial vessels (routinely used for definition of AIF). In turn TTP is directly determined from DSC signal time course and thus doesn’t require any assumptions about AIF which makes TTP parameter a good choice for unbiased characterization of tissue perfusion [20].

We found no significant differences between Cho/Cr ratios in GBM and pseudo-progression. This is opposite to reports which claim that Cho/Cr>2 are characteristic for tumor recurrences [33]. However there are studies that compromise ability of this ratio to distinguish pseudo-progression from tumor tissue [7]. It is a well-known fact that neither reduction in NAA/Cr ratio nor concentrations of NAA are specific in distinguishing brain pathologies [34].

Our findings suggest that excess glycine in region of post-contrast enhancement in treated GBM might pinpoint to rest/reappearance of tumor. To our knowledge there are no MR spectroscopic studies which had dealt with use of Gly levels in distinguishing of recurrent tumor from pseudo-progression. However, there are both biochemical [35] and MR spectroscopic studies [33,36,37] reporting increased glycine levels of GBM. There are several assumptions about origins of increased levels of this amino acid in high grade
tumors. The excess concentration of glycine found in GBM may be consequence of altered metabolism of glucose in which 3-phosphoglycerate follows alternative pathway being converted in 3-phosphoserine and further in serine and glycine [38]. Recently, Chinnayian et al [35] reported altered glucose metabolism in GBM and several-fold increase in levels of key metabolites glucose-6-phosphate, ribose-5-phosphate, serine and glycine. This finding could support previous assumption. In turn, increased levels of inhibitory neurotransmitter glycine may be response to excitotoxic levels of glutamate in extracellular space found in GBM tissue. Although some studies suggesting presence of additional gene mutations in RCT compared with primary GBM, so far there are no convincing evidences for differences in their chemical constitution. This supports our speculation that increased levels of glycine may be indication of presence of RCT.

One of the major limitations of our study is difficulty of precise estimation of Gly which may be hampered by the spectral overlap with the J-coupled resonances of Myo The J evolution of resonances during the echo time can be exploited for differentiation between the Gly and Myo signals [39] but it cannot be excluded a contribution from Myo even in long echo times.

Other potential limitation of our study is the difficulty in defining pseudo-progression. In our study, we defined pseudo-progression based on RANO criteria. These criteria were chosen to provide the most potentially useful information to the treating neuro-oncologist. It is possible that some of the patients who were classified as progressive disease due to a change in treatment, however, could have had pseudo-progression and done well. On the other hand, it is possible that some patients classified as pseudo-progression instead had slowly progressive tumors.

Our final analysis cohort was relatively small, with a low number of pseudo-progression patients. The magnitude in the differences in TTP parameter was striking, however statistical significance was achieved. This suggests that such differences between the two groups are real and robust enough to prompt additional, larger studies.

**Conclusions**

Non-invasive techniques to detect and quantify metabolic features and hemodynamic status of human tumor tissue have outstanding clinical potential in cancer imaging. Result implies that changes in Gly levels and TTP may be related to specific signatures that favor better response on therapy and outcome for GBM patients.


Figures

Fig. 1
Fig. 3a
Fig. 3b
Fig. 6
Legends

**Fig. 1** FLAIR and post-contrast T1W images obtained in the 10\textsuperscript{th} week after surgery in patients with true progression (upper row) and pseudoprogression (lower row). Although minute area of post-contrast enhancement was observed in b), the appearance of new lesions (not shown) observed in follow-up MRI in the 6\textsuperscript{th} month after surgery confirmed presence of true progression. In case of pseudoprogression follow-up MRI demonstrated decrease of region of post-contrast enhancement.

**Fig. 2** Relative cerebral blood volume values for pseudoprogression and recurrent tumor in 3\textsuperscript{rd} week and 10\textsuperscript{th} week after surgery.

**Fig. 3a** Average DSC curves in patients with tumor progression in 3\textsuperscript{rd} week (circles) and 10\textsuperscript{th} week (squares) after surgery.

**Fig. 3b** Average DSC curves in patients with pseudo-progression in 3\textsuperscript{rd} (circles) and 10\textsuperscript{th} week (squares) after surgery.

**Fig. 4** Time-to-peak values of progression and pseudo-progression in 10\textsuperscript{th} week compared with TTP values from normal brain tissue and contra-lateral brain tissue.

**Fig. 5** ROC curves of perfusion TTP for progression and pseudo-progression in A) 3\textsuperscript{rd} and B) 10\textsuperscript{th} week after surgery.

**Fig. 6** 1H MR spectra with long echo time in patients with a) pseudo-progression and b) progressive disease in 10\textsuperscript{th} week. Spectroscopic voxel was positioned in solid part of the tumor. On 6b glycine peak is present (3.56 ppm) in spectra of patient with diagnosed progression.

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