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Advanced MRI increases the diagnostic accuracy of recurrent glioblastoma: Single institution thresholds and validation of MR spectroscopy and diffusion weighted MR imaging

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ABSTRACT

The accurate identification of glioblastoma progression remains an unmet clinical need. The aim of this prospective single-institutional study is to determine and validate thresholds for the main metabolite concentrations obtained by MR spectroscopy (MRS) and the values of the apparent diffusion coefficient (ADC) to enable distinguishing tumor recurrence from pseudoprogression. Thirty-nine patients after the standard treatment of a glioblastoma underwent advanced imaging by MRS and ADC at the time of suspected recurrence — median time to progression was 6.7 months. The highest significant sensitivity and specificity to call the glioblastoma recurrence was observed for the total choline (tCho) to total N-acetylaspartate (tNAA) concentration ratio with the threshold ≥1.3 (sensitivity 100.0% and specificity 94.7%). The ADCmean value higher than 1313×10^{-6} mm^2/s was associated with the pseudoprogression (sensitivity 98.3%, specificity 100.0%). The combination of MRS focused on the tCho/tNAA concentration ratio and the ADCmean value represents imaging methods applicable to early non-invasive differentiation between a glioblastoma recurrence and a pseudoprogression. However, the institutional definition and validation of thresholds for differential diagnostics is needed for the elimination of setup errors before implementation of these multimodal imaging techniques into clinical practice, as well as into clinical trials.

1. Introduction

The critical biological characteristic of a glioblastoma (GBM), the most frequent and serious primary brain tumor in adults is an inevitable progression after standard therapy with the median of 6.9 months (Dusek et al., 2014; Stupp et al., 2005). Tumor recurrence develops in almost all patients despite the aggressive standard first line treatment, which comprised of radiotherapy and temozolomide usage (RT and TMZ) (Stupp et al., 2005). GBM recurrence, however, has often similar radiologic characteristics on conventional MRI as therapy-related changes, like a pseudoprogression (PsP). Thus, the early and accurate diagnosis of GBM relapse constitutes to be an important clinical need, especially when more and more potentially active drugs are currently being investigated for salvage treatment.

In comparison with standard structural MRI techniques, advanced imaging methods, such as diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, and the proton MR spectroscopy (MRS), allow much deeper and still non-invasive insight into the interpretation of brain lesions, resulting in greater specificity of diagnostic imaging (Ahmed et al., 2014; Bulik et al., 2015; Kao et al., 2013; Roy et al., 2013). In our previous report of the consecutive series of 24 patients with GBM, we described significant differences in ADC and MRS data between those with GBM relapse and PsP after standard RT and TMZ treatment (Bulik et al., 2015). However, thresholds with

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higher statistical power and intra-institutional validation have been required before these methods can be implemented into our institutional imaging protocols on a routine basis and used in the decision-making process. In this report, we present our final results of this prospective study with extended number of patients, as well as the results from an independent retrospective intra-institutional validation.

2. Methods

2.1. Characteristics of patients

Patients suitable for this study included the ones with histologically proven GBM after gross total resection, as stated by an early post-surgery MRI examination, who underwent the standard adjuvant treatment consisting of concurrent RT (dose 60 Gy) and TMZ followed by adjuvant TMZ alone (Stupp et al., 2009). The standard follow-up imaging protocol at our institution is the classic structural MRI after 6 weeks and every 3 months thereafter. Patients were eligible for study enrollment when suspected radiographic progression on the structural MRI was found based on the neuro-radiologist's discretion. After they signed an informed consent, the patients underwent the investigational advanced MRI, namely MRS and DWI. The final evidence of the disease status was realized by means of biopsy/resection or early repeated structural MRI depending on the clinical situation, patient's performance status, de facto his or her best interest. The advanced imaging protocol was approved by the Institutional Review Board of the St. Anne's University Hospital Brno. Patients previously described in our initial analysis are also included in the current study cohort (Bulik et al., 2015). The validation cohort consisted of the independent series of previous patients with GBM treated by surgery and adjuvant RT and TMZ, who underwent MRS and DWI/ADC exams according to the same protocol. Initially, the derived thresholds for pertinent MRS spectra and ADCmean values were subsequently applied to predict a GBM recurrence or treatment related changes, such as PsP and radionecrosis.

2.2. MR data acquisition

The advanced MRI examination was performed at 3.0T clinical MR scanner (GE Medical Systems Discovery MR750), following the same setup parameters as in our initial report (Bulik et al., 2015). MRS was focused on gadolinium-enhanced lesions suspected of recurrence by means of the chemical shift imaging (CSI) technique in two orthogonal planes respecting the long axis of the lesion and the proximity to structures increasing noise in MR spectra (point-resolved spectroscopy sequence — PRESS, TR/TE 1800/144 ms, 16-cm FOV, 15-mm slice thickness, and voxel size $10 \times 10 \times 15$ mm^3). Automatic prescanning was performed prior to each spectroscopic scan to ensure adequate water suppression. The MR spectra of all measured voxels were automatically post-processed for each patient by LCModel version 6.3 (Provencher, 2001). The output of MRS processing by LCModel were the concentrations of N-acetylaspartate and N-acetylaspartylglutamate (tNAA), choline-containing compounds (tCho), total creatine (tCr), lipids at 0.9–1.3 ppm, and lactate (Lac). Afterwards, the ratios of the metabolite concentrations (tCho/tNAA, tCho/tCr, tNAA/tCr, Lac + Lip1.3/tCr, Lac + Lip0.9–1.3/tCr) were calculated and visualized by jSIPRO 1.0 beta version (Jiru et al., 2013). The signal-to-noise ratio for each MR spectrum and an error map showing the error in a measured concentration for each metabolite were calculated by using the jSIPRO software. The concept of error images in jSIPRO was developed to help rejection of low quality spectra (Jiru et al., 2006). From the voxels covering gadolinium-enhancing region, these with the signal-to-noise ratio > 3 and the error of measured metabolite concentrations <20% where selected and arranged based on the value of the Cho/NAA ratio. The voxels with the highest Cho/NAA ratio were selected for further analyses.

An axial echo planar SE sequence (TR/TE 6000/100 ms), 5-mm slice thickness, and diffusion gradient encoding in three orthogonal directions ($b = 0$ and 1000 mm^2/s, and 240-mm FOV) were utilized for DWI imaging. ADC maps were calculated using the OsiriX software version 6.0.2 64-bit (Pixmeo SARL, Switzerland) with the ADC Map Calculation plugin version 1.9 (Stanford University). The mean ADC value (ADCmean) of the voxel corresponding to the measured MRS voxel was calculated.

2.3. Data analysis

The optimal diagnostic cut-offs and the description of their sensitivity and specificity for the final diagnosis of recurrence were derived from the receiver operating characteristic (ROC) analysis with the area under the ROC curve (AUC) for distinguishing between the two diagnostic groups (GBM relapse and PsP). Fisher's exact test for categorical data and Mann–Whitney *U* test for continuous variables were used to estimate the significance of measured differences. Censoring the patients who were lost for the follow up, the overall survival was defined as the time elapsed between the GBM diagnosis and death from any cause. The time to progression was measured since the end of RT and TMZ with suspected progression at structural MRI as the event of interest. The probability value $p < 0.05$ was considered statistically significant in all tests. All statistical evaluations were performed using the statistical software Statistica 12 (StatSoft, Inc.).

3. Results

3.1. Study patient characteristics

Between May 2013 and March 2015, the total of 39 patients (median age 51, 72% men) with suspected GBM progression on the structural MRI was prospectively included into this study. The basic characteristics of patients are summarized in Table 1. The median time to suspected progression and the median overall survival were 6.7 months (95% CI 2.9–9.6) and 14.5 months (95% CI 12.9–17.4), respectively. The final diagnosis was established by a biopsy in 26 patients (67%) and by follow-up imaging in 13 patients (33%). The diagnosis of a GBM recurrence yielded in 29 patients (75%) with the rest having PsP. No case of radionecrosis was found in our cohort of patients.

Table 1
Basic characteristics of the study cohort: T = temporal, F = frontal, P = parietal, O = occipital, F–P = frontoparietal, 3D-CRT = Three-Dimensional Conformal Radiotherapy, IMRT = Intensity-Modulated Radiotherapy.

Basic characteristics	*Study cohort* $n = 39$	*Validation* $n = 16$	*p*
Age at initial diagnosis (years)			
Median	51	54	0.7
Range	29–66	35–64	
Sex (n)			
Men	28 (72%)	10 (63%)	0.5
GBM location (%)			
T/F/P/O/F-P	38/29/19/5/9	34/31/14/7/14	0.7
Radiotherapy			
Median dose (Gy)	60	60	0.9
Technique 3D-CRT/IMRT (%)	30/70	40/60	0.8
Cycles of adjuvant TMZ			
Median	6	6	0.9
Range	1–12	4–10	
Time to graphic progression (months)			
Median (95% CI)	6.7 (2.9–9.6)	6.1 (4.8–8.8)	0.8
Diagnosis validation			
Biopsy/subsequent imaging (%)	67/33	75/25	0.6
Final diagnosis			
Tumor recurrence	29 (75%)	12 (75%)	1
Pseudoprogression	10 (25%)	4 (25%)	
Overall survival (months)			
Median (95% CI)	14.5 (12.9–17.4)	14.0 (13.1–15.2)	0.8