Magnetic Resonance Imaging 34 (2016) 803–808

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.mrijournal.com

Original contribution

Altered intraoperative cerebrovascular reactivity in brain areas of high-grade glioma recurrence

Jorn Fierstra [a,*], Bas van Niftrik [a], Marco Piccirelli [b], Jan Karl Burkhardt [a], Athina Pangalu [b], Roman Kocian [c], Antonios Valavanis [b], Michael Weller [d], Luca Regli [a], Oliver Bozinov [a]

[a] Department of Neurosurgery, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Switzerland
[b] Department of Neuroradiology, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Switzerland
[c] Department of Neuro-anesthesia, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Switzerland
[d] Department of Neurology, Clinical Neuroscience Center, University Hospital Zurich, University of Zurich, Switzerland

ARTICLE INFO

Article history:
Received 17 December 2015
Revised 17 January 2016
Accepted 1 February 2016

Keywords:
Functional MRI
Blood oxygen-level dependent
Intraoperative
High-grade cerebral glioma
Cerebrovascular reactivity

ABSTRACT

Introduction: Current MRI sequences are limited in identifying brain areas at risk for high grade glioma recurrence. We employed intraoperative 3-Tesla functional MRI to assess cerebrovascular reactivity (CVR) after high-grade glioma resection and analyzed regional CVR responses in areas of tumor recurrence on clinical follow-up imaging.

Methods: Five subjects with high-grade glioma that underwent an intraoperative Blood Oxygen-Level Dependent (BOLD) MRI CVR examination and had a clinical follow-up of at least 18 months were selected from a prospective database. For this study, location of tumor recurrence was spatially matched to the intraoperative imaging to assess CVR response in that particular area. CVR is defined as the percent BOLD signal change during repeated cycles of apnea.

Results: Of the 5 subjects (mean age 44, 2 females), 4 were diagnosed with a WHO grade III and 1 subject with a WHO grade IV glioma. Three subjects exhibited a tumor recurrence on clinical follow-up MRI (mean: 15 months). BOLD CVR measured in the spatially matched area of tumor recurrence was on average 94% increased (range − 32% to 183%) as compared to contralateral hemisphere CVR response, 1.50 ± 0.81 versus 1.03 ± 0.46 respectively ($p = 0.31$).

Conclusion: For this first analysis in a small cohort, we found altered intraoperative CVR in brain areas exhibiting high grade glioma recurrence on clinical follow-up imaging.

1. Introduction

Currently, the best available neuroimaging biomarker for identifying high grade gliomas is conventional contrast-enhanced magnetic resonance imaging (CE-MRI) [1]. The ability of obtaining this sequence with intraoperative MRI further enhances resection control by providing a timely evaluation of tumor residual that can be removed additionally [2–4]. CE-MRI sequences, however, are inherently limited to exactly identify tumor borders due to heterogeneous tumor enhancement and cannot assess functional parameters such as tumor molecular biology. Therefore, O-(2-[18F]fluoroethyl)-L tyrosine Positron Emission Tomography, (FET-PET) may potentially better depict high grade glioma tissue, but lower spatial resolution and limited clinical availability are remaining challenges [5].

Cerebrovascular reactivity (CVR) is a functional parameter that indicates remaining reserve capacity of the cerebrovascular autoregulation and can be assessed with MRI by obtaining Blood Oxygen-Level Dependent (BOLD) volumes [6]. CVR is determined as the BOLD signal response due to deoxyhemoglobin washout related to carbon dioxide (CO_2) changes as the vasoactive stimulus [7], and can be measured on high spatial resolution covering the entire brain. Using this concept, Hsu et al. [8] have demonstrated that BOLD MRI generates CVR patterns to better distinguish normal brain tissue from glioma tissue. Bashat et al. [9] used BOLD CVR to assess the effect of anti-angiogenesis tumor therapies in subjects with intracranial high-grade gliomas, and found that such an assessment can complement existing MR techniques for better detection and follow-up of angiogenic changes. Others have suggested that a BOLD-CVR examination may complement current functional task-based fMRI to identify areas of neurovascular uncoupling in patients with gliomas [10].

The use of intraoperative BOLD CVR for intracranial tumors has not been reported thus far. We hypothesized that intraoperative BOLD CVR is altered in perifocal non-contrast enhancing tissue prone

* Corresponding author at: Department of Neurosurgery, University Hospital Zurich, University of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland. Tel.: +41 44 2551111; fax: +41 44 2554505.
E-mail address: jorn.fierstra@usz.ch (J. Fierstra).

http://dx.doi.org/10.1016/j.mri.2016.02.003
0730-725X/

to future tumor recurrence. For this initial study we analyzed five consecutive subjects from an ongoing prospective intraoperative BOLD CVR study that underwent high-grade glioma resection. All subjects were postoperatively followed with clinical CE-MRI imaging. Three subjects exhibited a tumor recurrence within 2 years of follow-up. The area of tumor recurrence on follow-up CE-MRI was spatially matched with the intraoperative BOLD CVR data to assess CVR response in that particular area.

2. Materials & methods

2.1. Subject selection

This study was approved by the cantonal ethics board of the Canton of Zurich, Switzerland (KEK-ZH-Nr. 2012–0427). In October 2013 we have started an ongoing prospective study of intraoperative BOLD MRI CVR in subjects undergoing a cerebral glioma resection to assess regional CVR patterns. For this analysis, we selected subjects from this prospective database with high-grade glioma, defined as histopathological type III or IV according to WHO criteria, and a minimum of 18 months follow-up after tumor resection. Five consecutive subjects were found eligible.

The study protocol consisted of an additional BOLD MRI sequence with 3 cycles of apnea (i.e. CO_2 changes) during a scheduled intraoperative MRI examination following tumor resection. All subjects gave signed consent for study participation preoperatively. Subjects that were not able to sign consent were excluded as well as subjects with any predisposing cardio-pulmonary condition requiring special anesthetic care during surgery.

2.2. Intraoperative BOLD MRI imaging protocol

Mechanically ventilated subjects were scanned on a 3-Tesla Siemens Skyra VD13 (Siemens, Erlangen, Germany). Images were obtained using a customized intraoperative 8 channels head coil (NORAS MRI products, Hochberg, Germany), incorporated with an MRI compatible surgical four-point head-fixation system in which the subject's head was placed at surgery. Whole brain BOLD volumes were collected with an axial 7.20 min 2D echo planar imaging (EPI) BOLD sequence with voxel size: $3 \times 3 \times 3$ mm3, acquisition of matrix 64×64, 35 slices with ascending interleaved acquisition, slice gap 0.3 mm, GRAPPA factor 2 with 32 ref. lines, adaptive Coil Combination, Auto Coil Selection, TR/TE 2000/30 ms, flip angle 85°, bandwidth 2368 Hz/Px, 220 volumes, field of view 192 mm × 192 mm. For co-registration of the functional sequence, skull stripping and overlay purposes, the anatomical T1-weighted-MPRAGE sequence (Voxel size: $0.5 \times 0.5 \times 0.9$ mm, Field of View read 240 mm, Slice thickness 0.90 mm, TR 1900.0 ms, TE 2.60 ms, Flip angle 9 deg., Base resolution 256, Phase resolution 100%, Interpolation to 512×512) from the clinical protocol was used. The field of view from the BOLD image acquisition was copied to the T1-weighted image for better early realignment of both images.

2.3. CO_2 stimulus during BOLD acquisitions

BOLD signal changes were made by three cycles of apnea to induce hypercapnia (ie. higher CO_2 levels) under direct neuro-anesthetic monitoring. During the first 88 s, regular mechanically ventilated breathing was continued to provide a baseline, after which a 44 s apnea - breath hold - period was initiated by halting the ventilator. After apnea the subject was manually hyperventilated to swiftly return to baseline CO_2 value. In total, 3 identical series of 44 s apnea were done during the BOLD sequence with an interval baseline period of 88 s. A 44 s apnea paradigm is expected to provide a robust CO_2 change within physiological range [11]. Furthermore, following standard clinical management during intraoperative MRI examinations at our institution, subjects were continuously monitored by our neuro-anesthetic team.

2.4. Data analysis

The images were preprocessed using Statistical Parameter Mapping software (SPM 12, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London; http://www.fil.ion.ucl.ac.uk/spm/). A mean BOLD volume was calculated and the T1-weighted image was linearly registered to this volume. Automated segmentation of the T1-weighted image generated gray and white matter, cerebrospinal fluid, skull and skin probability maps. The BOLD images were smoothed with an $8 \times 8 \times 8$-mm full width half maximum Gaussian kernel. Due to the four point head fixation, we assumed that minimal head motion could occur during the MRI acquisition. Therefore, correcting for head-motion in realignment was not considered necessary. Temporal smoothing included a low pass filter of 0.125 Hz and robust Loess smoothing (dynamic local regression of 6%).

2.5. Cerebrovascular reactivity maps

MRI volumes were analyzed using in-house scripts written in MATLAB2013 (The MathWorks, Inc., Natick, United States; http://www.mathworks.com/). MR time-courses were detrended by fitting a linear series to the data. A Sine wave was created with a separate frequency for the apnea period and ventilation period. To increase coherence, we calculated the maximum Pearson product–moment correlation and shifted the Sine wave to its best fit with the BOLD data on a voxel-wise base [12]. After applying a combined gray and white matter mask with a threshold of 0.9, CVR, defined as the percent BOLD change, was then calculated using a voxel-wise linear regression of BOLD time series versus the Sine wave with least square fitting.

The resected tumor area matched the signal intensity of CSF and was automatically not included in the calculations. Hemispheres were manually segmented in left and right hemisphere and CVR was calculated separately for both. CVR maps were color-coded and overlayed on the T1-weighted image (Fig. 1).

2.6. Extended analysis

2.6.1. Intraoperative residual tumor

An experienced staff neuroradiologist (A.P.) determined the presence of residual tumor on intraoperative clinical MRI. When tumor residual was found present, we implemented an automated delineation process by extracting the T1-CE and T2 fluid-inversion attenuated recovery (FLAIR) images. For subject 3, no contrast enhancement was seen on T1, but diagnosis of recurrence was made based on FLAIR T2 imaging (Fig. 2). In summary, first, a linear registration was done to align the images using the T1-weighted image as the reference. Both T1-weighted images were normalized to their mean and standard deviation on a voxel-wise base which has been shown to improve contrast to noise in the images [13]. Thereafter, the normalized T1-CE was subtracted from the normalized T1-weighted to create the subtraction map (Fig. 2).

To determine solely pathological voxels (tumor residual), the FLAIR image was aligned with the subtraction image and normalized in a similar manner as both the T1-weighted images. This allowed for exclusion of physiological contrast-enhanced regions (large arteries, meninges) as well as exclusion of voxels outside of the brain on the T1-weighted subtraction map. After evaluation of these normalized maps, it was decided to threshold the FLAIR image at a fixed value of 5 to generate a binary mask only including voxels with FLAIR signal hyperintensities. To finally delineate the residual tumor, the binary