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Glioblastoma

Early and late effects of radiochemotherapy on cerebral blood flow in glioblastoma patients measured with non-invasive perfusion MRI

Jan Petr [a,*], Ivan Platzek [b], Annekatrin Seidlitz [c,g,h], Henri J.M.M. Mutsaerts [f], Frank Hofheinz [a], Georg Schramm [a,e], Jens Maus [a], Bettina Beuthien-Baumann [a,d], Mechthild Krause [c,g,h,i], Jörg van den Hoff [a,d]

[a] Helmholtz-Zentrum Dresden-Rossendorf, PET Center, Institute of Radiopharmaceutical Cancer Research, Dresden; [b] Department of Radiology, University Hospital Carl Gustav Carus; [c] Department of Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus; [d] Department of Nuclear Medicine, University Hospital Carl Gustav Carus, Technical University Dresden, Germany; [e] Department of Imaging and Pathology, Katholieke Universiteit Leuven, Belgium; [f] Brain Sciences Research Program, Sunnybrook Research Institute, Toronto, Canada; [g] OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technical University Dresden; and [h] German Cancer Consortium (DKTK) Dresden and German Cancer Research Center (DKFZ) Heidelberg, Germany; and [i] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology, Germany

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ABSTRACT

Background and purpose: To provide a systematic measure of changes of brain perfusion in healthy tissue following a fractionated radiotherapy of brain tumors.

Materials and methods: Perfusion was assessed before and after radiochemotherapy using arterial spin labeling in a group of 24 patients (mean age 54.3 ± 14.1 years) with glioblastoma multiforme. Mean relative perfusion change in gray matter in the hemisphere contralateral to the tumor was obtained for the whole hemisphere and also for six regions created by thresholding the individual dose maps at 10 Gy steps.

Results: A significant decrease of perfusion of −9.8 ± 20.9% ($p = 0.032$) compared to the pre-treatment baseline was observed 3 months after the end of radiotherapy. The decrease was more pronounced for high-dose regions above 50 Gy (−16.8 ± 21.0%, $p = 0.0014$) than for low-dose regions below 10 Gy (−2.3 ± 20.0%, $p = 0.54$). No further significant decrease compared to the post-treatment baseline was observed 6 months (−0.4 ± 18.4%, $p = 0.94$) and 9 months (2.0 ± 15.4%, $p = 0.74$) after the end of radiotherapy.

Conclusions: Perfusion decreased significantly during the course of radiochemotherapy. The decrease was higher in regions receiving a higher dose of radiation. This suggests that the perfusion decrease is at least partly caused by radiotherapy. Our results suggest that the detrimental effects of radiochemotherapy on perfusion occur early rather than later.

Radiotherapy (RT) as well as Radiosurgery (RS) are known to impair healthy tissue perfusion in various organs by damaging capillaries and larger vessels and impairing their autoregulation mechanisms [1]. Defects in cardiac perfusion measured with single-photon emission computed tomography (SPECT) using ^{99m}Tc were observed in patients with breast cancer treated with RT [2]. A large decrease of regional lung perfusion upto 80% was measured by SPECT in patients with tumors in the lung [3] or the thorax [4,5]. Cerebral blood flow (CBF) changes have also been demonstrated in healthy tissue after RS [6,7].

RT of the brain was also reported to cause a notable deterioration of cognitive performance [8,9] especially when delivered in daily fractions above 2 Gy [10] while other authors attribute the cognitive decline mainly to the presence of the tumor [11]. RT-induced CBF decrease would be one possible explanation for a cognitive decline. In any case, a detailed understanding of the relation between the received dose during RT and the CBF reduction is of obvious relevance for treatment planning as well as for diagnostic evaluation of the disease progression and for determining tissue specific dose tolerance levels.

CBF can be measured non-invasively by arterial spin labeling (ASL) which provides a facility for investigation of early and late radiochemotherapy (RCT) effects on healthy brain tissue on a population level. This may provide new insights into how the brain vasculature responds to RCT and clarify the correlation between CBF changes and neurocognitive changes.

So far, there are only very few publications studying the effect of RT and RS on CBF in healthy tissue which, moreover, report partly contradictory findings: Jakubovic et al. investigated the

* Corresponding author at: POB 51 01 19, 01314 Dresden, Germany.
E-mail address: j.petr@hzdr.de (J. Petr).

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dependence of perfusion changes on received dose during stereotactic RS. One month after treatment, the authors observed a significant CBF increase in gray matter (GM) in high-dose regions above 10 Gy [7]. Taki et al. studied CBF changes with ^{99m}Tc SPECT 2 weeks, and 3 months after RS of intracranial lesions. A significant CBF decrease was found in the regions with doses below 5 Gy [6]. A study by Weber et al. did not find any significant changes in the ratio of white matter (WM) to GM perfusion from 2 months to 1 year following RS with either dynamic susceptibility contrast (DSC) or ASL [12].

The aim of the present investigation is the quantitative assessment of CBF changes in healthy tissue during RCT and determination of the correlation between received radiation dose and induced CBF changes in order to augment the existing, partly contradictory literature and to contribute to the final clarification of this issue. For that purpose, data from a longitudinal study were used which is targeted at investigation of the degree of correlation between high [^{11}C]-Methionine tracer uptake in glioblastomas and time to recurrence after RCT. In this study, patients are scanned before postoperative radiooncological treatment and have regular follow-ups after the end of treatment. The perfusion was measured non-invasively using pseudo-continuous ASL (pCASL) [13,14]. To the best of our knowledge, the present investigation is the first systematic study addressing the effect of RT on healthy gray matter CBF as well as the first ASL-based study of perfusion changes following RT.

Materials and methods

Subject recruitment

All patients analyzed are part of a larger prospective, one-arm, single-center, non-randomized, observational imaging study – PETra trial (NCT01873469). The study was done in accordance with the declaration of Helsinki and it was approved by the Ethics Committee of the Faculty of Medicine at the Technische Universität Dresden (EK41022013). Data protection and patient informed consent procedures were done according to German national and state legislation.

Adult patients with newly diagnosed glioblastoma multiforme were included in the study if they fulfilled the following criteria:

- age more than 18 years, and signed a written informed consent to participate in the study,
- Karnofsky Performance Score $\geqslant$60 corresponding to performance score $\leqslant$2 according to the Eastern Cooperative Oncology Group (ECOG) [15,16],
- indication for combined RCT with Temozolomide (TMZ),
- histological confirmation of a glioblastoma multiforme,
- time interval between the last surgical procedure and onset of RCT no longer than 7 weeks.

Exclusion criteria were:

- previous radiotherapy of the brain or chemotherapy with TMZ,
- contraindications for RCT, or MRI imaging,
- known other malignant disease that impacts prognosis of the patient and/or is likely to require treatment interfering with study therapy.

Study design

The post-operative PET/MR and treatment planning CT were performed before the start of RCT. Irradiation treatment planning was done using a fusion of the planning CT with the PET/MR scan and with the postoperative MRI performed within 24 h after surgery. The RCT started 2–7 weeks after the tumor resection or biopsy. The second PET/MR scan was acquired 3 months after the end of RCT. Then, regular follow-up PET/MR scans were acquired every 3 months until objective detection of recurrence, death of the patient, or drop out.

Adjuvant radiotherapy was applied in daily fractions of 2 Gy given 5 days per week. The clinical target volume comprised the surgical cavity, macroscopic tumor areas visible in MRI or PET. A margin of 20 mm and 5 mm in all directions excluding anatomical barriers (bone, tentorium) was added in the first (CTV1) and second (CTV2) clinical target volume, respectively. CTV1 was treated to a total dose of 50 Gy. CTV2 received a boost dose of 10 Gy, adding to a total dose of 60 Gy.

Concomitant chemotherapy with TMZ (75 mg/m^2) was administered daily from the 1st day until the last day of radiotherapy followed by continuation of adjuvant chemotherapy for 6 months according to Stupp et al. [17]. Radiotherapy was delivered with linear accelerators providing photons of energies $\geqslant$6 MV. Field shaping was performed with a multileaf collimator. 3D-conformal radiotherapy plans were generated within a dedicated planning system. Intensity-modulated radiation therapy (IMRT) was used if appropriate with respect to target volume coverage or normal tissue sparing.

Acquisition

All MRI measurements were performed with a 3T Philips Ingenuity TF PET/MR scanner (Philips Healthcare, Best, The Netherlands) with an 8-channel head-coil. The following precautions to avoid CBF confounders were applied. Patients were instructed to be fasting 4 h prior to the scanning and were not instructed to change their habits regarding smoking and caffeine consumption.

A high-resolution T1-weighted isotropic 3D dataset, pCASL images, and M_0 reference images were acquired. The 3D TFE (Turbo Field Echo) T1-weighted dataset was obtained in the sagittal orientation with 1 mm isotropic resolution. Parameters of the pCASL sequence [18] were: field-of-view (FOV) 220×220 mm^2, voxel size $2.75 \times 2.75 \times 6$ mm^3, 17 slices (0.6 mm gap), 2D multi-slice gradient-echo echo planar imaging (EPI) readout, repetition time (TR)/echo time (TE) 3765/11 ms, flip angle 90°, 30 averages, background suppression [19] with optimal suppression timed for the lowest slice, labeling time/post-labeling delay (PLD) 1650/1525 ms. The delay between acquisition of successive EPI slices was 32 ms. The PLD for the central slice was thus equivalent to 1781 ms. A reference M_0 image was acquired 5000 ms after saturation. The center of the 5th or 6th slice (to ensure coverage of the whole cerebrum) was aligned with the anterior/posterior commissure line, and the distance of the center of the labeling plane from the lowest slice was 35 mm. A screen-shot of the planning was saved and the follow-up sessions were positioned similarly. The whole ASL acquisition took under 5 min.

A CT image for radiotherapy planning was acquired with a Siemens Emotion scanner (Siemens Medical Systems, Erlangen, Germany). The slice thickness was 3 mm and in-plane pixel size 1×1 mm^2.

Preprocessing and CBF quantification

Data were processed using the SPM8 toolbox (Wellcome Trust Centre for Neuroimaging, London, UK) and in–house routines written in Matlab (MathWorks, Natick, MA, USA). All pCASL dynamics and the M_0 measurement were registered to the first pCASL control image (3D rigid 6-parameter transformation with a sum-of-squares-differences cost function). For each patient and session, the T1-weighted image was co-registered with the mean pCASL control image. The T1-weighted image was segmented using SPM