Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Photon vs. proton radiochemotherapy: Effects on brain tissue volume and perfusion

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ARTICLE INFO

Article history:
Received 2 September 2017
Received in revised form 16 November 2017
Accepted 21 November 2017
Available online xxxx

Keywords:
Arterial spin labeling
Cerebral blood flow
Radiochemotherapy
Brain atrophy
Proton beam therapy

ABSTRACT

Background and purpose: To compare the structural and hemodynamic changes of healthy brain tissue in the cerebral hemisphere contralateral to the tumor following photon and proton radiochemotherapy.
Materials and methods: Sixty-seven patients (54.9 ±14.0 years) diagnosed with glioblastoma undergoing adjuvant photon ($n = 47$) or proton ($n = 19$) radiochemotherapy with temozolomide after tumor resection underwent T1-weighted and arterial spin labeling MRI. Changes in volume and perfusion before and 3 to 6 months after were compared between therapies.
Results: A decrease in gray matter (GM) (−2.2%, $P < 0.001$) and white matter (WM) (−1.2%, $P < 0.001$) volume was observed in photon-therapy patients compared to the pre-radiotherapy baseline. In contrast, for the proton-therapy group, no significant differences in GM (0.3%, $P = 0.64$) or WM (−0.4%, $P = 0.58$) volume were observed. GM volume decreased with 0.9% per 10 Gy dose increase ($P < 0.001$) and differed between the radiation modalities ($P < 0.001$). Perfusion decreased in photon-therapy patients (−10.1%, $P = 0.002$), whereas the decrease in proton-therapy patients, while comparable in magnitude, did not reach statistical significance (−9.1%, $P = 0.12$). There was no correlation between perfusion decrease and either dose ($P = 0.64$) or radiation modality ($P = 0.94$).
Conclusions: Our results show that the tissue volume decrease depends on radiation dose delivered to the healthy hemisphere and differs between treatment modalities. In contrast, the decrease in perfusion was comparable for both irradiation modalities. We conclude that proton therapy may reduce brain-volume loss when compared to photon therapy.
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Glioblastoma is the most common primary malignant brain tumor in adults. The standard therapy is maximal surgical resection followed by radiotherapy (RT) with concurrent and adjuvant chemotherapy using temozolomide [35]. Both RT and chemotherapy are, however, associated with risks of cognitive deficits and structural and hemodynamic changes in the normal brain tissue [3,1].

Brain atrophy may appear as a side-effect of RT and a progressive decrease in gray matter (GM) volume over time and a dependence on radiation dose have been reported after photon RT [29,18,17,32,33]. Interestingly, no significant changes in white matter (WM) volume were observed in the same studies, despite finding WM fiber damage following RT from diffusion MRI data [7,9].

RT was also shown to cause vessel-wall thickening and endothelial cell loss leading to cerebral microbleeds and occlusions in the microvasculature [24,25]. These changes could in turn affect the healthy-tissue perfusion. Several studies have investigated the

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https://doi.org/10.1016/j.radonc.2017.11.033
0167-8140/

influence of RT on brain perfusion with mostly contradictory conclusions. Perfusion decreases have been detected by dynamic susceptibility contrast and arterial spin labeling (ASL) MRI, and with ^{99m}Tc–HMPAO scintigraphy [36,28,27,11]; whereas perfusion increases have been measured using a computed tomography (CT)-perfusion, dynamic susceptibility contrast MRI, and ^{15}O-H_2O PET [22,14,15].

We posit that reduction in healthy tissue damage following radiochemotherapy (RCT) may be achieved using proton instead of photon RT. Proton therapy offers better dose distribution while exploiting comparable biological effectiveness [19]. In this study, we aimed to assess potential benefits of proton over photon therapy in terms of reducing damage to healthy brain tissue. We investigated the early-delayed brain volume and perfusion changes in healthy tissue at 3 and 6 months after RT, correlated the changes to the delivered radiation dose, and compared the differences between radiation modalities.

Methods

Participants and experimental design

The present investigation concerns the first two follow-up sessions of patients treated in the prospective, two-arm (photon and proton therapy), single-center non-randomized imaging trial "Observational study of impact of [^{11}C]-methionine PET/MRI as a tool for individual tailoring postoperative radiochemotherapy for patients with glioblastoma multiforme" (PETra). This trial was designed to validate the value of [^{11}C]-methionine PET as an imaging biomarker for predicting the location of recurrence as a basis for future radiotherapy dose-escalation approaches. Patient accrual lasted from September 2013 until October 2016 and the results according to the endpoints laid down in the protocol will be reported separately.

The registered trial (NCT01873469) was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine at the Technische Universität Dresden, Germany (EK41022013). All patients provided written informed consent.

The main inclusion criteria of the PETra trial included newly diagnosed glioblastoma, age $\geqslant$18 years and Karnofsky's Performance Score $\geqslant$60. After clinical introduction of proton-beam therapy at the University Proton Therapy Dresden at December 2014, the choice of treatment with photon or proton-beam therapy depended on the decision of the treating physician, the patient and on reimbursement of the costs. The current investigation included only those patients for which MRI scans prior to initiation of RCT were available, who had unilateral tumor localization before RCT, who received all planned fractions of photon- or proton-beam irradiation, and who were scanned at least once after the end of RCT. In total, 72 patients (51 photon, 21 proton) were included in this imaging study (mean age 54.3 ± 14.2 years, range 23.2–81.8 years, 29 female).

The first MR session was performed after surgery and before start of RCT. For each patient, imaging data also included [^{11}C]-Methionine PET and treatment-planning CT scans. RT treatment started 2–7 weeks after full or partial tumor resection or biopsy. After the end of RT, follow-up MRI scans were acquired every 3 months for two years or until disease progression or drop out of the patient. Here we present follow-up data at 3 and 6 months after the end of RT.

Radiation treatment planning was based on the CT and PET/MRI scans. The margin of the clinical target volume (CTV) around the surgical cavity and macroscopic tumor was 20 mm for the volume treated up to 50 Gy (2 Gy per fraction) and 5 mm for the boost volume treated with an additional 10 Gy (2 Gy per fraction) to a total dose of 60 Gy (60 GyE for proton therapy). A 5 mm margin was added for the planning target volume.

Photon-based radiation treatment plans were generated using either 3D conformal radiotherapy(3DCRT) (Oncentra Masterplan 3.1, Nucletron, Veenendaal, The Netherlands; $n = 27$) or intensity-modulated radiotherapy (IMRT) (Pinnacle 9.0, Philips, Eindhoven, The Netherlands; $n = 24$). Photon RT was delivered with linear accelerators with multileaf collimator (Siemens Healthcare, Erlangen, Germany) providing photons of energies 15 and 6 MV. Proton beam treatment plans were generated using passive double scattering technique (XiO, Nucletron) and therapy was delivered with a cyclotron providing energies of 100 MeV–230 MeV.

Concomitant chemotherapy with the cytostatic agent temozolomide was performed according to Stupp et al. [35].

Image acquisition

All imaging was performed on a 3T Philips Ingenuity TF PET/MRI scanner (Philips Healthcare, Best, The Netherlands) with an 8-channel head-coil.

On each session, a 3D Turbo Field Echo T1-weighted (T1w) image was acquired with a $1 \times 1 \times 1$ mm^3 resolution. A pseudo-continuous ASL sequence [10] with background suppression [12] was used to acquire perfusion-weighted images as described in detail previously [27]: voxel size $2.75 \times 2.75 \times 6$ mm^3, 17 slices (0.6 mm gap), 2D echo-planar-imaging readout, TR/TE 3765/11 ms, 30 averages, labeling time 1650 ms, post-labeling delay for the first and last slice 1525 and 2037 ms, respectively. An M_0 image was acquired with TR 5000 ms.

Preprocessing and perfusion quantification

All image processing was fully automatic and was done using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK), and in-house routines written in Matlab (MathWorks, Natick, MA, USA) based on ExploreASL, with specific modifications to accommodate brain deformations by the tumor and surgery.

The T1w image was segmented using SPM12 [4] with enhanced tissue priors [21] providing a relative content of GM, WM, and CSF in each voxel, see Supplementary Fig. 1B. To avoid the bias in segmentation caused by the presence of tumor and surrounding edema, both hemispheres were segmented separately. The T1w image was rigid-body co-registered with the mean ASL control image. Perfusion defined as regional cerebral blood flow (CBF) was quantified from the raw ASL data using the single compartment model [2] and provided voxel-wise in mL/min/100 g, see perfusion maps in Supplementary Fig. 1D.

For the pre-therapeutic sessions, the CT image with the radiation dose map was co-registered to the T1w image as shown in Supplementary Fig. 1. For the post-therapeutic sessions, the T1w images were non-linearly registered to the pre-therapeutic T1w images [5] to allow regional comparison of dose and volumes across sessions.

Imaging data exclusion

ASL images were examined by two researchers (JP, HM) with 7 years of experience in ASL image processing. Images with severe motion or acquisition artifacts were excluded from further analysis.

T1w images were examined by a radiologist (IP) with 12 years of experience. Images with severe motion artifacts, which could lead to false decreases in GM volume [30], were excluded. Post-RCT sessions with new morphological findings in WM compared to the pre-RCT baseline (e.g. edema, leukoencephalopathy) were also excluded.

Please cite this article in press as: Petr J et al. Photon vs. proton radiochemotherapy: Effects on brain tissue volume and perfusion. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2017.11.033