Normal and tumoral brain vessel response to Microbeam Radiation Therapy

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Rationale and objectives

Microbeam radiation therapy (MRT) is based on the principle of spatial fractionation instead of clinically-used temporal fractionation. MRT-damaged micro-segments in the poorly differentiated neovasculature of brain tumors may not be efficiently repaired, leading to tumor asphyxia and necrosis, in contrast to the rapid repair of radiation-damaged normal microvasculature by minimally irradiated cells surviving in the tissue slices situated between the microbeams (1-3). The aim of this work is to study the normal and tumoral vessel response after microbeam exposure using magnetic resonance imaging and synchrotron micro-tomography.

Methods

Thirteen days after inoculation, rat 9L gliosarcomas implanted in nude mice were irradiated using two orthogonal arrays of 28 planar microbeams (width 25µm, interbeam spacing 211µm, microbeam entrance dose: 500 Gy). At different time intervals after MRT (1, 7, and 14 days after MRT i.e., 14, 21 and 28 days after implantation) apparent diffusion coefficient (ADC), blood volume (BV) and vessel size index (VSI) were mapped at 2,35T on anesthetized animals using a diffusion MR sequence and a multiple gradient echo-spin echo MR sequence, the latter images being acquired before and after injection of Sinerem® (200-300 µmol Fe/Kg). Two regions of interest were defined: whole tumor and contralateral hemisphere. An ANOVA test was used to compare different data groups. The effects of a 25 µm microbeam width, cross-fired exposure on 9L brain tumor and normal vessels in rats were imaged using x-ray micro-tomography on ID19. At 2, 7 and 14 days after MRT (performed 14 days after implantation), an intra-cardiac perfusion of soluble, micron sized, barium sulfate particles was performed. Normal brain tissue and tumor samples (~3 mm diameter x ~7 mm high) were sampled from excised rat brains. Synchrotron micro-tomography was performed using 21 keV photons (1500 angles) on tumor samples with a 1.4 µm pixel size.

Results

At any time after implantation, ADC, BV and VSI were higher in tumoral tissue than in contralateral hemispheres. A significant increase in ADC values has been observed 24 hours after MRT in irradiated tumors ($1081 \pm 73 \times 10^{-6}$ mm².s^{-1}) versus unirradiated ones ($978 \pm 81 \times 10^{-6}$ mm².s^{-1}) ($p<0.001$). This increase could be attributed to a radiation induced increase in tumoral blood vessel permeability. Micro-tomographic tumor vessel imaging reveals significant regions of barium sulfate diffusion in the extravascular compartment 2 days after irradiation. This constitutes an interesting illustration of the impact of MRT on tumor vessels. Normal brain vessels, located in the contralateral hemisphere and irradiated unidirectionally, did not present direct signs of contrast agent

leakage on micro-tomographic images. Furthermore, significant change in ADC was found in normal brain tissue using MRI measurements. A change in tumor vessel organization could be observed on vascular network images. Indeed, qualitative examination realized 14 days after irradiation revealed that vessel density was sensibly decreased and VSI measured by MRI increased significantly between 14 and 28 days after implantation (+26% ($p<0.01$)). Furthermore, there was no significant change in tumor blood volume measured by MRI whatever the observation delay, consistently with micro-tomographic tumor imaging which shows that tumor vessels remain perfused within the two weeks following microbeam exposure.

Conclusion

This study reports and illustrates for the first time the effect of MRT brain tumor vessels. It shows that MRT increases tumor vessel permeability during the first days after exposure. This observation could be exploited to deliver cytotoxic or anti-angiogenic agents specifically to tumor tissue via the circulatory system since normal brain vasculature is not drastically damaged by microbeam exposure. However, no significant change in tumor blood volume was detected consistently with micro-tomographic images which show that tumor vascular networks remain perfused after irradiation. This study also suggests that MRT parameters could be optimized to cause major damage to tumor vessels.

References

[1] Dilmanian FA, Button TM, Le Duc G, *et al.* Response of rat intracranial 9L gliosarcoma to microbeam radiation therapy. *Neuro-oncol* 2002;4:26-38.

[2] Laissue JA, Geiser G, Spanne PO, *et al.* Neuropathology of ablation of rat gliosarcomas and contiguous brain tissues using a microplanar beam of synchrotron-wiggler-generated X rays. *Int J Cancer* 1998;78:654-660.

[3] Slatkin DN, Spanne P, Dilmanian FA, *et al.* Subacute neuropathological effects of microplanar beams of x-rays from a synchrotron wiggler. *Proc Natl Acad Sci U S A* 1995;92:8783-8787.