Cerebral edema induced by Synchrotron Microbeam Radiation Therapy in the healthy mouse brain. Characterization by means of Diffusion Tensor Imaging.

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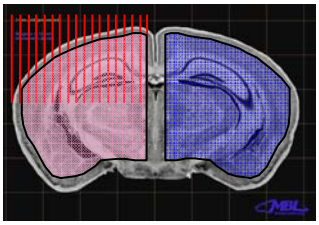
INTRODUCTION:

Conventional radiotherapy of brain tumors may induce significant necrosis and edema in the surrounding healthy brain, which can be characterized by modification of the Apparent Diffusion Coefficient (ADC) [1]. Microbeam Radiation Therapy (MRT) is a new preclinical, therapeutic tool using synchrotron x-rays. It may significantly reduce radiation damage in the healthy brain tissue by spatial microfractionation of the absorbed radiation dose [2,3]. It is hypothesized that non-irradiated endothelial cells located between the irradiated zones are able to repair the microvascularisation and/or the Blood Brain Barrier (BBB) in the irradiated zones. Thus, MRT might limit radiation induced brain edema given a rapid repair of the BBB. The aim of this work was to assess brain edema by analyzing early MRT effects (1day – 1 month) on normal brain tissue using Diffusion Tensor Imaging (DTI) and microgravimetric methods.

MATERIAL AND METHODS:

Healthy Swiss NUDE mice, 5 weeks old, 14-24 g weight were anaesthetized with xylazine/ketamine (0,1%/1%, 10 µl per g of body weigth). They were irradiated at the ESRF (European Synchrotron Radiation Facility, Grenoble, France) with x-rays at 312 and 1000 Gray in the antero-posterior direction by 18 microplanar-beams of 25 µm width and separated by 211 µm peak to peak in the left cerebral hemisphere (Fig. 1). At different times after irradiation (1, 7, 14, 21, and 28 days, n=5 for each delay and dose) mice were anesthetized with xylazine/ketamine (0.1%/1%, 10 µl per g of body weigth) and placed in a stereotactic cradle. Body temperature was maintained at 37°C using warm water circulating through a pad. DTI was performed at 7T. Diffusion gradients were applied in six different orientations: ((Gx,Gy,Gz): (1,0,0); (0,1,0); (0,0,1); (1/√2)(1,1,0); (1/√2)(1,0,1); (1/√2)(0,1,1)). *b* value was 500s/mm^2, *TE/TR* = 40/2500ms. Diffusion time ($\Delta-\delta/3$) was 17 ms and diffusion gradients were applied during 8ms (δ). 5 slices (1.5 mm thick) were acquired (NAV = 4) with a *FOV* of 12 mm and a matrix size of 64 x 64. Average values of ADC were calculated on two regions of interest (whole irradiated hemisphere as well as the contralateral counterpart respectively purple and blue on Fig. 1). At the same delays after microbeam exposure, the Cerebral Water Content (CWC) was determined by the microgravimetric method [4]. Wilcoxon and one-tailed Mann-Whitney tests were used to compare groups of data (*: p<0.05).

Fig. 1: Irradiated scheme (red) and Regions of Interest (purple and blue)



RESULTS AND DISCUSSION:

ADC histograms from brain hemispheres at different delays post MRT are presented in Figs. 2, 3 and 4 for irradiations at 312 Gy and 1000 Gy [5]. ADC values in contralateral and in irradiated hemispheres are not significantly different, except in the group of animals 1 day post 312 Gy radiation. A significant decrease of the ADC is then observed (8%, p<0.05, left shift of the irradiated ADC on the histogram Fig. 2) as well as a tendency to increased CWC (+0.38% in irradiated hemisphere), likely reflecting the presence of a weak cytotoxic edema [6] in the irradiated region. This edema is resorbed 14 days after radiation exposure (Fig. 3: no shift on histogram). These observations have been correlated with *in vivo* biphoton microscopy imaging which does not reveal BBB crossing of small molecules (Sulforhodamine B, 0.58 kDa) after a 312 Gy MRT [7].

At a higher radiation dose (1000Gy; Fig. 4: no shift on histogram), none of the ADC values show significant differences (no or mixed edema [6]). However, *in vivo* biphoton microscopy studies revealed diffusion of Sulforhodamine B through the BBB, providing evidence of vasogenic edema secondary to BBB breakdown after a 1000 Gy radiation treatment [7]. Moreover, microgravimetric analysis shows significant increase of CWC at day 1 post MRT in the irradiated hemisphere (+0.68%, p<0.05). These results could reveal the simultaneous presence of cytotoxic and vasogenic edemas.

CONCLUSION:

DTI and microgravimetric method allow monitoring and characterization of induced MRT brain edema. Minor and transient cellular edema has been detected 1 day after 312 Gy microbeam radiation. Previous MRT studies at the same dose on implanted gliosarcomas have shown a good therapeutic index [2], indicating that MRT is a promising tool in the treatment of malignant brain tumors while preserving healthy tissue.

Fig. 2 : ADC histogram of contralateral and irradiated brain hemispheres 1 day after 312 Gy irradiation.

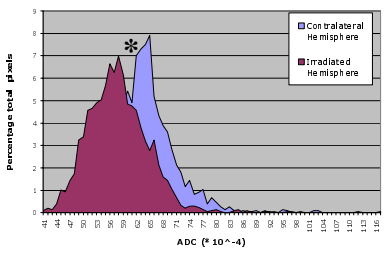


Fig. 3 : ADC histogram of contralateral and irradiated brain hemispheres 14 days after 312 Gy irradiation.

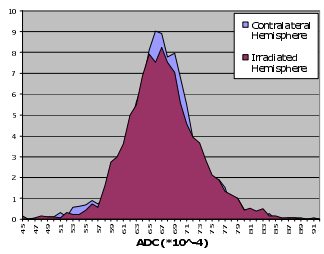
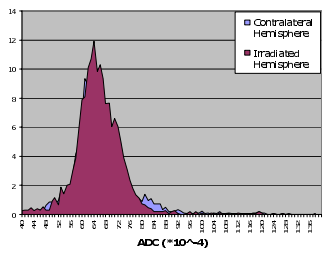


Fig. 4 : ADC histogram of contralateral and irradiated brain hemispheres 1 day after 1000 Gy irradiation.



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