Characterization of microbleed formation from normal brain microvasculature after radiation therapy

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Introduction

Radiotherapy (RT) is an integral component in the management of patients with glioma, but the damage that it may cause to healthy brain tissue function and impact upon quality of life is of concern [1]. The histologic response to radiation includes vasculopathy, with progressive impairment in cerebral microcirculation and formation of cavernous angiomas that may slowly or acutely hemorrhage. In a prior study, we used Susceptibility-Weighted Imaging (SWI) [2] to evaluate the long-term effects of radiation therapy on normal-appearing brain tissue in 20 patients with gliomas and demonstrated that microbleeds appeared in irradiated patients after two years from receiving therapy, that the prevalence of these lesions increased over time since receiving radiation therapy, and that they often extended outside the T2-lesion and into the contralateral hemisphere [3]. Microbleeds were not observed in patients who were only treated with chemotherapy. The lack of serial imaging data in that study meant that there was limited information available to describe the initial evolution of these lesions. The primary goal of the current study was to use SWI to characterize the evolution of microbleeds in normal-appearing brain tissue that result from radiation therapy on an individual patient basis. Since anti-angiogenic drugs are thought to have a radio-protective effect on the existing vasculature and recent studies have administered bevacizumab prior to hypo-fractionated RT [4], our second aim was to determine whether the concomitant administration of an anti-angiogenic agent altered the process of microbleed formation due to irradiation.

Methods

SWI data from twelve patients with glioma (9 grade 4, 2 grade III, 1 grade 2), who were scanned serially for 2-13 time points from 9 months to 4.5 years, were retrospectively analyzed for this study. All patients received external beam radiation therapy (x-RT) with adjuvant chemotherapy. Six of the 12 patients (all newly-diagnosed GBM) were also treated with an adjuvant PKC-inhibitor anti-angiogenic therapy. High resolution T2*-weighted SWI was acquired on a 3T GE EXCITE scanner with an 8-channel phased array receive coil using a 3D flow compensated SPGR sequence with TE/TR 28/56ms, flip 20°, 24cm FOV, 512x144 image matrix with GRAPPA R=2 plus 16 autocalibrating lines, and an in-plane resolution of 0.5 x 0.5mm and 2mm slice thickness. Standard SWI post-processing was performed on the reconstructed k-space data for each coil, and then combined, intensity corrected, and projected through 8 mm-thick slabs. Microbleeds were identified as discrete foci of susceptibility that did not correspond to vessels or hemosiderin staining of the surgical cavity on consecutive slices. The number of microbleeds was counted in normal-appearing tissue, outside the tumor region and any areas of acute hemorrhage. The resulting data were plotted as a function of time since RT.

Results & Discussion

Serial within-patient analysis: For the patients receiving RT+anti-angiogenic therapy there were enough serial scans to assess evolution of mirocbleeds on an individual basis. In this case, the number of microbleeds was found to increase linearly with time (Fig. 1), with the initial onset being anywhere between 9 and 22 months, depending on the patient being considered.

Rates of microbleed formation: Group analysis between the rate of microbleed appearance before 2 years post-RT versus after 2 years was performed on patients who did not receive anti-angiogenic therapy. Microbleeds were found to appear at a faster rate after 2 years than before (see Fig. 2). This was evident by both an increase in the slope of the best-fit line for all patients who received RT only when grouped together, as well as a statistically significant increase in the individual per-patient rates of change for all patients (Fig 2., inset). One patient (purple circles, Fig. 1) was excluded from the latter analysis due to rapid increase in microbleeds before 2 years post-RT that were far away from the site of the tumor.

Tracking of individual microbleed characteristics: No trends between microbleed size and time of appearance were observed. Three types of microbleeds were found, as shown in Fig. 3: (1) *stable*- remaining the same size once they appear (Fig. 3A); (2) *enlarging*- increasing in size over time (Fig. 3B); or (3) *large & stable*- initially appearing with a diameter of several mm and then remaining that size (Fig. 3C). Individual patients in either group could possess any combination of these types of microbleeds. Some microbleeds appeared in locations where there was no prior visible vasculature, while others directly stemmed from the deterioration of a larger neighboring vessel (Fig. 3D).

Effects of concurrent anti-angiogenic therapy: A trend toward less microbleeds in patients with anti-angiogenic therapy was observed in terms of both the rate of microbleed appearance after 2 years (Fig. 2) and the number of microbleeds present in all binned time periods (Fig. 4). This supports the existing hypothesis that anti-angiogenic drugs may have a radioprotective effect on microvasulature but the magnitude of the differences require the recruitment of more patients in order to reach statistical significance.

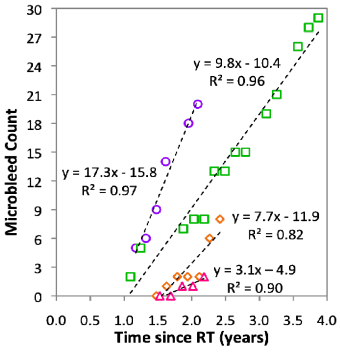

Fig 1. Plot of evolution of microbleeds for the individual patients who were scanned for at least 5 time points.

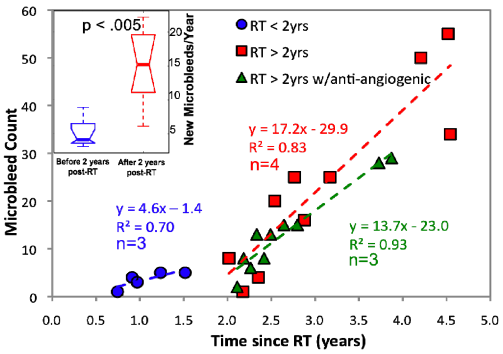

Fig 2. Rates of microbleed appearance over time before and after 2 years from exposure to radiation. The top-left inset shows boxplots of these rates between the 2 groups.

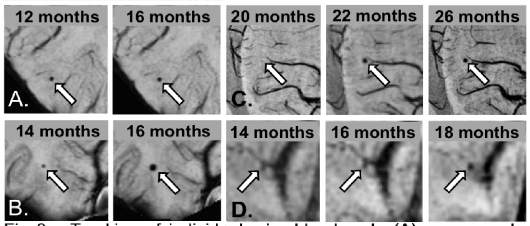

Fig 3. Tracking of individual microbleeds. In (A), an example where a microbleed stays the same size in 4 months; in (B), one that increases in size after only 2 months; in (C) one that appears at the larger size but does not grow; in (D) the deterioration of a surrounding vessel once a microbleed forms.

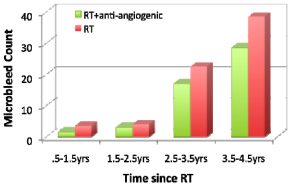

Fig 4. Comparison of microbleed appearance between patients with standard of care RT+chemotherapy and RT + chemo + anti-angiogenic therapy. The bars represent median microbleed counts within each year.

Conclusions

We have demonstrated that the appearance of hemosiderin-containing microbleeds increases linearly as a function of time since receiving radiation therapy. After 2 years, the rate of microbleed formation increases nearly 4-fold compared to microbleeds that appear before 2 years post-RT. The addition of an anti-angiogenic therapeutic agent appeared to slow down this processes. The size of the microbleeds varied both within and across patients with time. The ability to detect the onset and characterize the evolution of these lesions in normal brain tissue may be important in determining which parts of the brain are most susceptible to radiotherapy, and in further understanding the utility of such treatment in patients with lower grade tumors, who have relatively long survival. Future studies will focus on quantifying the size and spatial distribution of these lesions over time and correlating the number and location of microbleeds with radiation dose and presence of neurocognitive deficits.

References

[1] Karim A et al. *Int J Radiat Oncol Biol Phys* 2002;52(2):316-324,
[2] Haacke EM et al. *AJNR* 2007;28(2):316-7.
[3] Lupo JM et al. *Proc. 18th ISMRM* 2010.
[4] Gutin PH et al. *Int J Radiat Oncol Biol Phys* 2009;75(1):156-163.

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