Relating Radiation Dose to Microbleed Formation in Patients with Glioma

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Introduction

Radiotherapy (RT) is an integral component in the management of patients with glioma, but the damage that it can cause to healthy brain tissue function and impact upon quality of life is of concern.[1] The histologic response to radiation initially shows characteristic vascular changes associated with vasculopathy that later result in the formation of ferritin- or hemosiderin-containing deposits in the form of microbleeds that accumulate around vessels and, on histopathological analysis, reflect a spectrum of microvascular injury that includes endothelial damage, fibrinoid necrosis, luminal narrowing, and occlusion.[2] Our prior studies using Susceptibility-Weighted Imaging (SWI) have characterized both the extent and time course of these lesions and suggest that the addition of an anti-angiogenic therapeutic agent can slow down their rate of appearance in the first 2 years[3,4]; however, the relationship between microbleed characteristics and RT dose received has not been assessed. The goal of this study is to investigate the effects of RT dose on microbleed characteristics such as number, size, and rate of appearance in patients with glioma.

Methods

Serial SWI data from 17 patients with glioma (14 grade IV, 2 grade III, 1 grade II), who were scanned serially between 1 to 2.5 years from receiving RT, were retrospectively analyzed for this study. All patients received external beam RT with adjuvant chemotherapy. Eleven of the 17 patients (all newly-diagnosed GBM) were also treated with either an adjuvant anti-VEGF (5/11) or PKC-inhibitor (6/11) anti-angiogenic (AA) 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 contrast-enhancing tumor on consecutive slices and outlined using in-house software. For 7 patients (5 of whom received adjuvant AA therapy), radiation dosimetry maps were reconstructed on a Philips Pinnacle treatment planning system and fused with the SWI images that were acquired 22-28 months post-RT, after alignment to the original treatment CT images using an algorithm based on mutual information[5]. This time frame was selected to both maximize the number of patients included and allow for substantial microbleed formation. The aligned dose maps were segmented into high- (>60 Gy), mid- (45-60Gy), and low- (30-45Gy) dose regions according to standard clinical practice. The number of microbleeds within each dose region was normalized by the volume of brain tissue included in that region to compare microbleed counts between regions across patients. The rate of microbleed formation during the first two years was correlated to the sum of the mid- and high- dose volumes, while individual microbleed size was correlated to dose received across all patients combined. The effect of dose on microbleed formation over time was evaluated in one patient who had three serial SWI scans 2-4.5 years after receiving RT.

Results & Discussion

Microbleed Density and Dose: At 2 years post-RT, increases in microbleed density (count/volume of irradiated tissue) with dose were observed across patients. As shown in Figure 1A, a significant reduction in microbleed density was observed in the low-dose region compared to the combined mid- and high- dose regions (p=.03, Wilcoxon signed rank test). An increase in microbleed density between low-dose and high-dose regions for all patients individually was observed, although significance was not reached due to the small sample size (Wilcoxon signed rank test, p=.1) .

Rate of Microbleed Formation and Dose Volume: The rate of microbleed formation between 1 and 2 years post-RT was highly correlated to the size of the mid- plus high- dose region (Spearman rank correlation, r=.97, p<.005) as shown in Figure 1B. The importance of the extent of the mid- dose field is further emphasized in the two example patients shown in Figure 1C.

Microbleed Size and Dose: Although certain individual microbleeds were observed to increase in size over time, no correlation was found between individual microbleed size and dose. This is likely attributed to the large variability in microbleed size observed in AA patients, especially in the high dose region.

Long-term Effects of Dose over Time: As shown in Figure 1D, although microbleeds initially appear in high dose regions, more microbleeds emerged in lower dose regions over time.

Impact of Anti-angiogenic Therapy: At two years post-RT, no apparent difference was observed between therapy groups in the low dose region. A trend towards more microbleeds within the high dose region was observed in patients with adjuvant AA therapy, but more patients will be necessary to determine the significance of this observation.

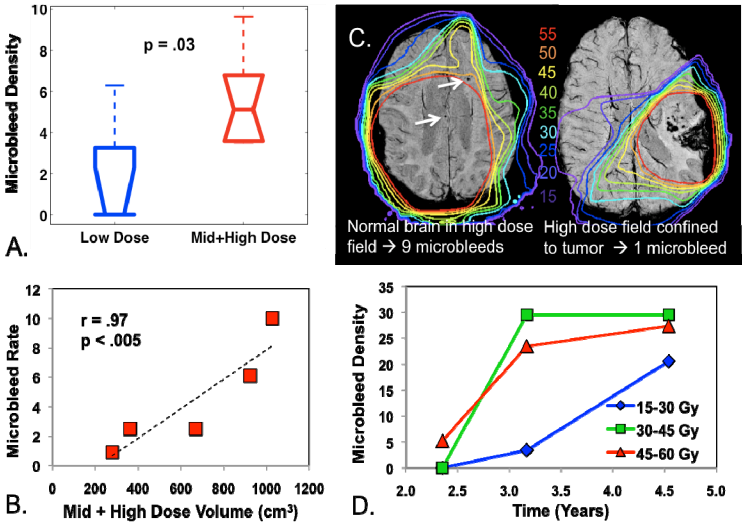

Figure 1. In A, microbleed density in low dose vs mid- plus high- dose regions. In B, correlation of the rate of microbleed formation with mid- plus high- dose regions. In C, contoured dose maps overlaid on SWI images. In D, microbleed density for different dose regions over time in a single patient followed serially.

Conclusions

We have demonstrated that the appearance of radiation-induced, hemosiderin-containing microbleeds is dependent upon dose of radiation received. At 2 years post-RT, an increase in microbleed density was found in higher dose regions. The rate of initial formation was highly dependent upon the volume of dose >45 Gy the tissue received. However, the size of an individual microbleed varied irrespective of dose received. The ability to detect these lesions and characterize their relationship with dose received to normal-appearing 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. Further implications of this study will be important in the management of brain tumor patients when considering therapeutic strategies, planning target volumes, evaluating prognosis, and assessing cognitive outcome.

References: [1] Karim A et al. *Int J Radiat Oncol Biol Phys* 2002;52(2):316-324, [2] Fajardo LF. Acta Oncol. 2005;44(1):13-22. [3] Lupo JM et al. Int J Radiat Oncol Biol Phys. Epub 2011 Oct 12. [4]Lupo JM et al. *Proc. 19th ISMRM* 2011. [5] Jenkinson M. et al *NeuroImage* 2002;17(2):825-841.

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