Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2012 March 1; 82(3): e493–e500. doi:10.1016/j.ijrobp.2011.05.046.

7 Tesla Susceptibility-Weighted Imaging to Assess the Effects of Radiation Therapy on Normal Appearing Brain in Patients with Glioma

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Abstract

Purpose—The potential effects of radiotherapy on neurocognitive function and quality of life are of great significance in patients with brain tumors. In this study we have used 7T Susceptibility-Weighted-Imaging (SWI) to evaluate the intermediate- and long-term imaging manifestations of RT on normal-appearing brain tissue in patients with treated gliomas.

Methods and Materials—7T SWI was performed on twenty-five patients with stable gliomas. Microbleeds were identified as discrete foci of susceptibility that did not correspond to vessels. The number of microbleeds was counted within and outside of the T2-hyperintense lesion. For three patients, radiation dosimetry maps were reconstructed and fused with the 7T SWI data.

Results—Multiple foci of susceptibility consistent with microhemorrhages were observed in patients two years following chemoradiation. These lesions were not present in patients who were not irradiated. The prevalence of microhemorrhages increased with the time since completion of radiotherapy, and these lesions often extended outside the boundaries of the initial high-dose volume and into the contralateral hemisphere.

Conclusions—High-field SWI has potential for visualizing the appearance of microbleeds associated with long-term effects of radiotherapy on brain tissue. The ability to visualize these lesions in normal-appearing brain tissue may be important in further understanding the utility of this treatment in patients with longer survival.

Keywords

radiation therapy; susceptibility-weighted imaging; 7 Tesla; brain tumor; treatment effects

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Introduction

Although radiotherapy (RT) is an integral component in the management of patients with glioma, its effects on neurocognitive ability and quality-of-life (QOL) are not fully understood (1). Following maximal safe resection, external beam radiotherapy to a 2 cm margin around the surgical cavity and residual tumor is a standard component of treatment for high-grade glioma and recurrent low-grade glioma. The width of these margins is based upon the histologic observations that malignant cells are frequently present at a distance of more than 3 cm from the contrast-enhancing margin, and that more than 80% of relapses occur within a 2 cm margin of the original contrast-enhancing tumor (2–4). Although the goal is to restrict the prescribed radiation dose, 60 Gy over the course of six weeks, to this defined region, to the residual tumor and peri-tumoral margins, surrounding healthy brain tissue can receive up to 30Gy at a distance of up to 10 cm away from the leading edge of the enhancing tumor. Even with modern technology, in order to include all potential locations of tumor infiltration, it is estimated that approximately 60% of tissue within the high-dose treatment field represents normal-appearing brain parenchyma (5). Treatment strategies for grade II lesions, whose target volumes tend to be large, are even more controversial because of concerns of injury to normal brain tissue, and patients in whom gross-total surgical resection is achieved are frequently observed until there is imaging or clinical evidence of progression before instituting adjuvant therapy.

Since modern RT delivery technologies now allow for spatially selective, modulated treatment plans, it is of utmost importance to identify the underlying pathogenic mechanisms of brain injury and find biological correlates that can measure these changes non-invasively. Microscopically, the histologic response to radiation initially shows characteristic vascular changes and white matter pathology ranging from demyelination to coagulative necrosis, as well as cortical atrophy and endothelial proliferation (6). More recent findings implicate the development of arteriopathy in the intermediate and long-term horizons following radiation, with resulting progressive impairment in cerebral microcirculation and formation of cavernous angiomas that may slowly or acutely hemorrhage (7). The clinical manifestation of these events usually begins anywhere from 9 months to several years after receiving RT, followed by presentation of obvious neurological deterioration many months or even years later. MR imaging findings have revealed changes in blood vessel permeability (8), the volume of T2-hyperintensity (9), and fractional anisotropy values within normal-appearing white matter (10, 11) during the first six months after the completion of radiotherapy.

SWI is able to visualize microvasculature and is a powerful tool for detecting hemosiderin- or ferritin-containing microbleeds (12,13). Microhemorrhages have been observed in several studies involving stroke and vasculopathic related injury using this technique (13–19). At 7T, heightened susceptibility effects provide enhanced sensitivity to detecting these lesions (16, 20–21). The goal of this study was to evaluate the potential of 7T SWI for studying the intermediate- and long-term effects of RT on normal-appearing brain tissue by assessing the number and location of the appearance of microbleeds as a function of time since treatment. It is hypothesized that radiation induced-damage to microvasculature will result in the formation of microhemorrhages visible on high-resolution 7T SWI images, the number of which, will increase with time. Whenever possible, the frequency of these lesions was compared to prior RT dose delivered to that location.

Methods

Patient Population

Twenty-five adult patients with stable gliomas of various grades, who were scanned at a total of 30 time points, were included in this retrospective study. In order to be eligible,

patients were required to have a Karnofsky Performance Score of ≥ 70 and no sign of tumor progression. All patients provided informed consent in accordance with guidelines established by our Institutional Review Board.

MR Imaging Acquisition

High-resolution SWI was performed on a GE whole-body 7T scanner (GE Healthcare Technologies, Milwaukee, WI) with volume excitation and 8-channel phased-array reception (Nova Medical, Wilmington, MA). A 3D SPGR sequence was applied with TE/TR=16ms/50–80ms, flip angle=15–20°, BW=62.5kHz, 24×24cm² FOV, and 1–2mm slice thickness. To keep the scan time under 6 minutes, a GRAPPA-based parallel imaging acquisition was utilized with either a 2- or 3-fold reduction factor, 512×144 acquired matrix, 0.5×0.5mm in plane resolution and 16 autocalibrating lines (22). The coverage in the S/I direction varied based on the acquisition and the extent of the tumor, resulting in scan times that ranged from 4.5–6.5 minutes. Phase imaging, using a 2D GRE sequence with 512×512×10 matrix, 22×22cm² FOV, slice-thickness/gap=2/2mm, TE/TR=11.4/250ms and NEX=3, was also performed and used to confirm the absence of calcification in these lesions, since SWI cannot distinguish between paramagnetic microbleeds and diamagnetic calcifying lesions. The 7T imaging protocol also included the acquisition of a low-resolution, proton-density-weighted, fast gradient-echo sequence for coil sensitivity estimation.

Standard clinical pre- and post-gad T1-weighted 3D SPGR and T2-weighted FLAIR images were acquired for anatomic comparison on a 3T GE scanner with 8-channel head coil immediately after the 7T exam. These images were used to identify regions of contrast enhancement and T2-hyperintensity, which were later overlaid on the co-registered SWI images.

Data Processing and Analysis

The complex k-space data from all 8 channels of the 7T SWI scan were transferred off-line and post-processing was performed using in house programs developed with Matlab 7.0 software on a Linux cluster. Standard SWI post-processing was performed on the reconstructed k-space data for each coil, combined, intensity corrected, and projected through 8 mm-thick slabs (16). Phase images were created as previously described by our group (23).

Microbleeds were identified as discrete foci of susceptibility that did not correspond to vessels or surgical cavity on consecutive axial slices. The number of hypointense spheres or microbleeds was counted within the entire SWI volume, within T2-hyperintense regions peripheral to contrast-enhancing tumor (T2L), outside of the T2L, and within the hemisphere contralateral to the treated tumor. In order to minimize user error from counting, microbleeds from each dataset were labeled and iteratively counted multiple times, until the same number of counts was obtained from two consecutive trials. The maximum number of iterations required for all patients was four. The total number of microbleeds was correlated with age, grade, pathology, presence of symptoms, and location of the tumor using a Spearman Rank correlation.

For three AC patients whose radiation treatment plans were available as digital data, radiation dosimetry maps were reconstructed on a Philips Pinnacle treatment planning system and fused with the 7T SWI data after alignment to the original treatment CT images using an algorithm based on mutual information (24). Contours were created at 10% intervals for dose gradations and displayed as a percent of the maximum dose.

Results

Patient Characteristics

Patient age ranged from 29 to 71 years (median age 48 years) at the time of imaging. According to the World Health Organization (WHO) II criteria, 8 patients had histologically-confirmed grade II gliomas (2 astrocytomas, 1 oligodendroglioma, 4 mixed oligoastrocytomas, and 1 ependymoma); 15 patients were classified as having grade III gliomas (4 anaplastic astrocytomas, 6 anaplastic oligodendrogliomas, 3 mixed anaplastic oligoastrocytomas, and 2 ependymomas); and 2 patients had grade IV gliomas (all glioblastoma multiforme).

Nineteen patients received prior external beam RT, either with or without adjuvant chemotherapy, between 1 and 20 years prior to the time of imaging. Six patients, four of whom were only treated with chemotherapy from 1–6 years prior to imaging, and two of who received no additional therapy post surgical resection, were scanned as controls. For the patients who received RT, the median time from completion of RT was 4.7 years. Contrast enhancement was present on the T1-weighted images of seven patients. Thirteen of the patients had tumors located in the right hemisphere, 7 patients had left hemispheric tumors, and 5 patients had tumors that involved both hemispheres. Eight of the 12 patients who had received RT between 1–6 years prior to imaging presented with new neurological deficits, while all of the control patients were asymptomatic at imaging.

Lesion Counts and Location

7T SWI scans revealed an increase with time from RT in the total number of microbleeds and the percent of microbleeds that resided outside the T2L, as shown in Figures 1 and 2. Patients who did not receive RT did not exhibit microbleeds as far as 6 years from onset of treatment (Figure 1, top panel and Figure 2A). Only 2 lesions in total were found in the 5 patients who received RT within two years of the scan date. Less than 10 microbleeds were observed in each of the 4 patients who received RT within 2.5 years of the SWI scan, 87% of which resided within the T2L, and all were located in the same hemisphere as the initial tumor. In the one patient who was scanned serially (Figure 3), no lesions were observed at 1.6 years, 6 were observed at 2.4 years, and 25 at 3.2 years post-RT, despite radiographic stability of the tumor. After 3 years, as shown in Figures 2B and 4, the presence of these lesions extends beyond the T2L and into the contralateral hemisphere. A larger variation in the number of these lesions as a function of time across patients was observed after 5 years post-RT as shown in Figure 2(A&C). No correlations were found between the number of microbleeds and age, grade, pathology, presence of symptoms, or location of the tumor.

Lesion Location and Radiation Dose

For three patients who received radiation at our institution, dosimetry maps were reconstructed and overlaid on the 7T SWI images. Visual inspection of the co-registered images showed a larger burden of microhemorrhages within regions that received highest doses of radiation, with the majority of microbleeds residing within the 90% isodose volume. Figure 5 illustrates the effect of RT dose on the location of microbleeds for two patients with similar microbleed counts. Figure 5A shows a grade II oligoastrocytoma 4.7 years post completion of RT with 28 total microbleeds (13 of which were in the T2L), where the 50% of the maximum dose isoline was contained to one hemisphere. In contrast, Figure 5B is an example of a grade III oligodendroglioma 3.2 years post-RT with 25 total microbleeds (14 of which were in the T2L) where the 50% isodose contour extends well into the contralateral hemisphere. As expected, the patient in Figure 5A had 5 microbleeds in the contralateral hemisphere within the 50% dose region, while patient in Figure 5B did not

exhibit any microbleeds contralaterally. The third patient, whose dosimetry maps are not shown, was only 2 years post-RT and did not yet have any microbleeds outside the T2L.

Discussion

Fractionated RT is the standard treatment for all patients with newly-diagnosed grade III and IV gliomas after surgical resection, and may be applied at a later stage for patients with grade II glioma who show signs of progression or recurrence. Total radiation dose is limited by late toxicity, which can manifest as neurocognitive decline. Understanding the temporal evolution of the effects of radiation on normal-appearing brain parenchyma is therefore an important consideration in the management of such patients and the determination of endpoints that describe outcome.

Because of their longer progression-free survival of 3–7 years (25) and earlier age at onset of disease, patients with grade II and grade III glioma are more likely to experience neurocognitive deficits from RT than patients with more aggressive tumors such as grade IV glioma (26). It has been argued that the standard clinical trial endpoints of survival and time to progression may be inadequate for quantifying outcomes for patients with glioma (27,28). Both the tumor itself and treatment effects can impact brain function and may compromise the patient's QOL. This is especially critical for patients who have long survival and for whom the late effects of radiation become relevant. It has been reported that glioma survivors maintain a relatively good performance status in the absence of recurrence but that they may experience a progressive decline in neurocognitive and psychological function following RT, with patients treated with more focal brain irradiation having improved outcome (28,29). The current neurocognitive frameworks for understanding changes in QOL over time requires further refinement and would benefit from the development of imaging biomarkers of radiation effects in order to gain additional insights into the pathogenesis of treatment-related brain injury. To date, there have been no definitive studies to identify specific brain regions that are most vulnerable to radiotherapy, although some authors have suggested that the hippocampus may be particularly sensitive to RT (29–33), and that visual attention and memory are disproportionately impaired in late radiation damage (28, 34–36).

Phase-sensitive and SWI techniques are powerful tools for imaging microvasculature and iron-containing hemorrhagic foci (13–15). Microbleeds appear as hypointense foci in T2*-weighted magnitude images due to intravoxel dephasing in and around the microbleed. The dephasing is caused by B_0 field distortion from iron containing compounds in venous blood. SWI is a post-processing technique that multiplies a masked, high-pass filtered phase image into the magnitude image to increase contrast by reducing signal intensity in susceptibility-shifted structures such as veins and microbleeds. Although the phase image is more accurate in quantifying the size of a structure if it is larger than the voxel size, when the anatomy of interest is smaller than the voxel size, the “blooming” effect in the magnitude image aids in detection. Using SWI for the current application is advantageous in that it utilizes information from both the magnitude and phase images, allowing the detection of large and small microbleeds without the need to vary the voxel size. At 7T, heightened susceptibility-effects provide enhanced sensitivity to these lesions (20,21), which we have shown is useful for examining the onset of subtle changes in normal brain tissue after exposure to radiotherapy.

Paramagnetic and diamagnetic field effects, which distinguish iron-laden blood products from calcification, can be differentiated using phase imaging but not with SWI. This is because both paramagnetic and diamagnetic field shifts cause signal dropout and therefore hypointense signal on SWI images, while diamagnetic calcifications appear hyperintense on phase images. Distinguishing calcium from blood products is clinically relevant in cases

where apparent blood products are actual pathological calcification or where apparent benign physiological calcification is actually pathological hemorrhage, but there is no biological evidence that would suggest the presence of calcification due to treatment effects. In this study, we used phase images to confirm that our lesions were in fact iron-containing microbleeds and not calcification. Only one of the 812 total identified lesions was determined to be a calcifying lesion and was therefore excluded from the analysis. This lesion was also much larger than all the other true microbleeds.

The preliminary results from high-resolution 7T SWI images presented in this manuscript suggest that radiation induced-damage to microvasculature results in the formation of microbleeds. These microbleeds began appearing approximately 2 years after the completion of radiotherapy in all patients scanned around this time, and only 2 patients had a single microbleed before 2 years. This time course of microbleed evolution is similar to histologic vascular changes observed in a group of healthy rodent brains irradiated with a single dose of 30–50Gy using a converging photon beam technique (37), and other reported delayed radiation vascular injuries (38). The vast majority (87%) of the 17 total microbleeds observed in patients that received RT within 2.5 years were located within the T2-lesion. This is most likely due to the fact that the standard definition of the treatment planning target volume contains the T2-hyperintense region plus a 2cm margin and doses are specified such that at least 95% of the PTV receives the prescribed dose. Thus, it is not surprising that this high dose region is where microbleeds initially appear. After 3 years post-RT, microbleeds begin to emerge beyond the T2-hyperintensity, most likely where the tissue was treated with a lower dose of radiation and would thus require a longer period of time for the vasculature to experience the same damage. It is also possible that normal-appearing brain parenchyma surrounding the current T2-lesion was initially hyperintense at the onset of treatment, and therefore received a higher dose as well.

A larger variation in the number of microbleeds among patients was observed after 7 years post-RT, suggesting that differences in the extent of radiation dose received to healthy brain tissue plays a major role in microbleed formation. The degree to which a treatment plan can conform to the margins of the tumor, and thus spare normal brain tissue, is highly dependent on the anatomical location of the tumor, its shape, and the capabilities of the radiotherapy system. Because this was a retrospective study, patients were treated over the course of a 20-year time period at various institutions, often before some of the recent advances in RT technology such as intensity-modulated RT. Therefore, patients treated more than 7 years ago likely experienced greater variations in the amount of dose administered to healthy tissue than those treated more recently. It is also possible that some anatomical structures are more susceptible to RT than others, as determined to be the case for the hippocampus (39,40) and neurogenic centers in the subgranular and subventricular zones (41).

Besides the inherent variation among RT treatment plans, the main source of error which contributed to the variability of microbleed counts over time was the differences in scan coverage due to the retrospective nature of this study. Images that were acquired earlier on in this study did not have the same full brain coverage later achievable as the study progressed with the development of more robust parallel imaging routines that allowed for increased coverage within the same scan time. This was an issue for 7 patients who had microbleeds that were at the edge of the imaged volume and, therefore, possibly more that extended beyond the covered region. Despite this limitation, the volumetric nature of SWI ensured that differences in microhemorrhage counts at different time points in the same patient were not simply due to partial volume averaging. Moreover, imaging in all cases was targeted to the tumor and surrounding T2 signal abnormality, which included the largest number of microhemorrhages.

A less likely contributor to the variation in microbleed counts is human error in lesion identification. The high conspicuity of both veins and microbleeds made it challenging to separate microbleeds from perpendicular veins using automated methods. Although care was taken to avoid these vessels by examining consecutive slices above and below the plane of each microbleed, misidentification of perpendicular veins as microbleeds was possible. The contiguous slice coverage of the 3D scan and minimum-intensity projections limited this source of error. Additionally, all scans were angled in parallel with the anterior commissure-posterior commissure, or AC-PC, line of the corpus callosum on a sagittal slice of the brain. This way, the percentage of perpendicular vessels, and therefore any errors in categorization, would be relatively consistent among patients.

In conclusion, we have demonstrated that high-field SWI has potential for visualizing the appearance of hemosiderin containing microbleeds associated with long-term effects of radiotherapy on brain tissue. The prevalence of these lesions increases over time since receiving RT. The ability to visualize these lesions in normal brain tissue may be important in further understanding the utility of this treatment in patients with grade II and grade III tumors with longer survival time. Future studies will involve longitudinal follow-up with serial imaging to investigate additional physiological changes due to treatment, and correlate the number and location of microbleeds and other imaging parameters with radiation dose and neurocognitive decline. The knowledge gained will be instrumental in planning future target volumes for irradiation, as well as understanding the temporal effects of radiation on the brain and which brain areas are more susceptible to radiation injury.

Acknowledgments

The authors would like to thank Douglas Kelley, Duan Xu, Daniel Vigneron, Jason Crane, and Beck Olson for their technical assistance with scanning or post-processing regarding this manuscript. We would also like to acknowledge Bert Jimenez, Kathryn Hammond-Rosenbluth, Colleen Cloyd, Gabriela Bourne, Trey Jalbert, Niles Bruce, and Mary McPolin for their help with scanning and data collection.

This study was supported by UC Discovery grants LSIT01-10107 and ITL-BIO04-10148 with GE Healthcare, NIH grants R01-CA059880 & P50-CA97257, and a Joelle Syverson American Brain Tumor Association Fellowship.

Conflicts of Interest Notification Grant support for this research was funded by a UC Discovery grant with GE Healthcare. This funding was awarded for the technical development of imaging sequences on a 7-Tesla system and in no way influences the clinical findings described in this manuscript.

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Figure 1.

7T SWI (left) and 3T T2-FLAIR (right) images of (A) a grade II oligoastrocytoma 4 years post-chemotherapy, (B) a grade III ependymoma 2 years post-RT, (C) a grade II oligoastrocytoma 4 years post-RT, and (D) a grade III oligoastrocytoma 8 years post-RT. Red arrows denote microhemorrhages.

Figure 2.

Plots of microbleed counts over time. (A) Total lesion count as a function of time for all patients who received RT (circles) and did not receive RT (squares) for all patients individually (*left*) and binned by years (*right*). (B) Percentage of microbleeds found outside the T2-lesion (T2L, triangles) and extending into the contralateral hemisphere (diamonds) as a function of time since RT for each individual RT patient (*left*) and when clustered by time (*right*).

Figure 3.

Example of a patient with a grade III oligodendroglioma scanned serially. Microhemorrhages do not appear until over 2 years after having received radiation. The number of hemorrhages quadruples after 3 years post-RT.

Figure 4.
Example of a grade III oligodendroglioma ~12 years post-RT with hemorrhages located both within and beyond the T2-lesion.

Figure 5. Radiation dosimetry contour lines overlaid on 7T SWI images. In (A), a grade II oligoastrocytoma 4.7 years post completion of RT with none of 28 total microbleeds in the contralateral hemisphere. In (B), a grade III oligodendroglioma 3.2 years post-RT with 5 of 25 total microbleeds existing in the contralateral hemisphere.