International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Central Nervous System

7-Tesla Susceptibility-Weighted Imaging to Assess the Effects of Radiotherapy on Normal-Appearing Brain in Patients With Glioma

Janine M. Lupo, Ph.D.,* Cynthia F. Chuang, Ph.D.,† Susan M. Chang, M.D.,‡ Igor J. Barani, M.D.,† Bert Jimenez, R.N.,* Christopher P. Hess, M.D., Ph.D.,* and Sarah J. Nelson, Ph.D.*,§

*Departments of *Radiology and Biomedical Imaging, †Radiation Oncology, ‡Neurosurgery; and §Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA*

Received Jan 5, 2011, and in revised form May 19, 2011. Accepted for publication May 20, 2011

Summary

7T susceptibility weighted imaging was used to evaluate the intermediate- and long-term effects of radiation therapy on normal-appearing brain tissue in 25 patients with gliomas. Microbleeds appeared 2 or more years after radiation therapy and their prevalence increased over time, often extending well beyond the initial high-dose volume and into the contralateral hemisphere.

Purpose: To evaluate the intermediate- and long-term imaging manifestations of radiotherapy on normal-appearing brain tissue in patients with treated gliomas using 7T susceptibility-weighted imaging (SWI).

Methods and Materials: SWI was performed on 25 patients with stable gliomas on a 7 Tesla magnet. 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 3 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 2 years after 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: Radiotherapy, Susceptibility-weighted imaging, 7 Tesla, Brain tumor, Treatment effects, Microbleeds

Reprint requests to: Janine M. Lupo, Ph.D., University of California, San Francisco, Department of Radiology and Biomedical Imaging, Byers Hall UCSF, Box 2532, 1700 4th Street, Suite 303, San Francisco, CA 94158. Tel: (415) 514-4420; Fax: (415) 514-1028; E-mail: janine.lupo@ucsf.edu

This study was supported by University of California Discovery Grants LSIT01-10107 and ITL-BIO04-10148 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); National Institutes of Health Grants R01-CA059880 and P50-CA97257; and a Joelle Syverson American Brain Tumor Association Fellowship.

Conflicts of interest: none.

Acknowledgment—The authors thank Douglas Kelley, Duan Xu, Daniel Vigneron, Jason Crane, and Beck Olson for their technical assistance with scanning or postprocessing regarding this article; and Kathryn Hammond-Rosenbluth, Colleen Cloyd, Gabriela Bourne, Trey Jalbert, Niles Bruce, and Mary McPolin for their help with scanning and data collection.

Int J Radiation Oncol Biol Phys, Vol. 82, No. 3, pp. e493–e500, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.05.046

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). After maximal safe resection, external-beam RT 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 on 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 6 weeks, to this defined region, to the residual tumor and peritumoral margins, surrounding healthy brain tissue can receive up 30 Gy at a distance of up to 10 cm away from the leading edge of the enhancing tumor. Even with modern technology, 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 2 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.

Because 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 noninvasively. 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 after 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 neurologic deterioration many months or even years later. Magnetic resonance 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 6 months after the completion of RT.

Susceptibility-weighted imaging (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 appearances 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 with prior RT dose delivered to that location.

Methods and Materials

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. To be eligible, patients were required to have a Karnofsky performance score of $\geq$70 and no sign of tumor progression. All patients provided informed consent in accordance with guidelines established by our institutional review board.

MRI acquisition

High-resolution SWI was performed on a GE whole-body 7T scanner (GE Healthcare Technologies, Milwaukee, WI) with volume excitation and eight-channel phased-array reception (Nova Medical, Wilmington, MA). A three-dimensional (3D) spoiled gradient echo (SPGR) sequence was applied with echo time/repetition time (TE/TR) of 16 ms/50–80 ms, flip angle 15–20°, bandwidth 62.5 kHz, 24 × 24-cm^2 field of view, and 1–2-mm slice thickness. To keep the scan time under 6 min, a generalized autocalibrating partially parallel acquisition was used with either a two- or threefold reduction factor, 512 × 144 acquired matrix, 0.5 × 0.5-mm in-plane resolution, and 16 autocalibrating lines (22). The coverage in the superior–inferior direction varied according to the acquisition and the extent of the tumor, resulting in scan times that ranged from 4.5 to 6.5 min. Phase imaging, using a two-dimensional gradient echo sequence with 512 × 512 × 10 matrix, 22 × 22-cm^2 field of view, slice thickness/gap of 2/2 mm, TE/TR of 11.4/250 ms, and number of excitations = 3, was also performed and used to confirm the absence of calcification in these lesions, because 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-gadolinium T1-weighted 3D SPGR and T2-weighted fluid attenuated inversion recovery images were acquired for anatomic comparison on a 3T GE scanner with eight-channel head coil immediately after the 7T examination. These images were used to identify regions of contrast enhancement and T2 hyperintensity, which were later overlaid on the coregistered SWI images.

Data processing and analysis

The complex k-space data from all eight channels of the 7T SWI scan were transferred off-line, and postprocessing was performed using in-house programs developed with MATLAB 7.0 software (MathWorks, Natick, MA) on a Linux cluster. Standard SWI postprocessing 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).