Justification and Feasibility of Neural Stem Cell Sparing in Whole Brain Irradiation Using VMAT

Radiation therapy is commonly used in the treatment of primary and metastatic brain tumors. However, normal tissue tolerance is limiting and radiation doses must be tailored to minimize the deleterious late effects of radiation on the central nervous system (eg. Cognitive decline). Efforts to reduce radiation induced cognitive decline are of particular clinical relevance given that no effective treatments are currently available (Roman et al, 1995). Cognitive decline manifests as learning and memory deficits, which are strongly influenced by the activity of neural stem cells and their proliferative progeny (Broadbent et al, 2004). These endpoints were observed following local irradiation of the rat brain (Hodges et al, 1998) suggesting that stem cell sparing during radiation therapy planning may help mitigate radiation induced cognitive decline.

Some studies have begun to focus on the deleterious effects of radiation on the central nervous system, and specifically have begun to address the role of stem cells (Barani et al, 2007). However, with the introduction of VMAT, it may be possible to better spare the neural stem cell compartment while providing whole brain and metastatic coverage. Further, it is unknown which neural stem cell response (cell death, differentiation or vascular changes), are most important in cognitive function post irradiation. Additionally, it is unclear at what radiation dose neural stem cells are most negatively affected. Thus we have examined both cell death and differentiation at clinically relevant radiation doses (0-6Gy).

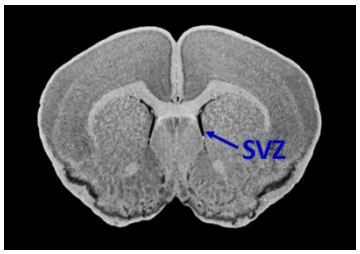
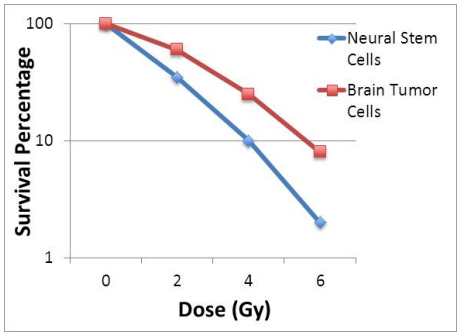


Figure 1: Neural stem cells are harvested from the sub-ventricular zone (SVZ) of the mouse brain, which lies along the lateral walls of the lateral ventricles.

To establish the relative radio-sensitivity of neural stem cells we performed clonogenic survival assays on both neural stem cells, harvested from the murine SVZ (Figure1) and brain tumor stem cells derived from the murine PTEN$^{-/-}$/Kras^{+} spontaneous brain tumor model. The neural stem cells were significantly more radiosensitive than their tumor stem cell counterparts (2Gy, p=0.018) (Figure 2A), and thus ideally should receive significantly less radiation than the tumor in order to minimize cognitive impairment while maintaining tumor control. In fact, at the clinically relevant dose of 2Gy, the brain tumor cells had nearly twice the surviving fraction as the neural stem cells (60% vs 35%).

A.



B.

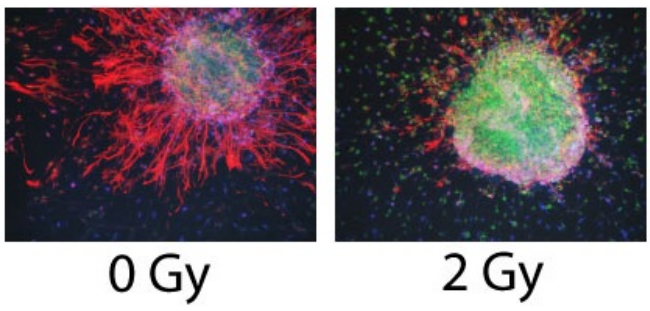


Figure 2: Radiation effects on neural stem cells.
A) Neural stem cells are more radiation sensitive than brain tumor cells. B) Radiation reduces the potential for neuronal differentiation in neural stem cells that survive irradiation (neurons shown in red).

Further, neural stem cells contribute to learning and memory function by continual proliferation and restructuring through neuronal differentiation. Here we show that the neuronal differentiation capacity of neural stem cells that survive radiation treatment is diminished (Figure 2B). Since both neural stem cell death and diminished differentiation ability result from radiation treatment, and likely play a role in radiation induced cognitive decline, we examined the feasibility of neural stem cell sparing using VMAT (Figure 2). The stem cell compartment was defined as the lateral ventricles with a 3-5mm margin. We observed that VMAT is able to maintain good whole brain coverage, while also reducing dose to the stem cell compartment. Conventional whole brain irradiation performed using 3D techniques does not allow for any sparing of the neural stem cells, thus cognitive decline is typically associated with conventional 3D whole brain radiation therapy. IMRT has been proposed as a means of stem cell sparing (Barani et al, 2007), however, better sparing and more conformal whole brain therapy, with the possibility of boosting the dose to large metastasis or tumors, may be possible using VMAT. We compared 3D, 7-field IMRT and VMAT for several patients receiving whole brain irradiation. VMAT provided the best neural stem cell sparing while maintaining adequate whole brain coverage with the shortest treatment delivery time.

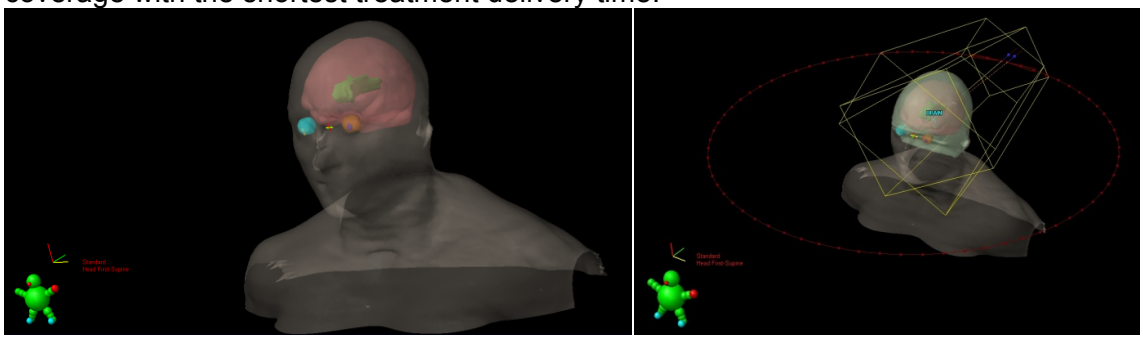


Figure 3: Sample VMAT plan geometry. The stem cell compartment is designated and contoured as the lateral ventricles with a 3-5mm margin (green).

We show here that radiation at relatively low dosage (2 Gy) highly affects both survival and differentiation ability of neural stem cells. Radiation induced cognitive decline is likely due to both neural stem cell death and compromised differentiation ability. Thus, our data support the continued investigation into sparing of neural stem cells in order to provide clinical management of cognitive dysfunction. Further, in order to explore new treatment options for brain tumors in which long-term survival and treatment induced neuro-cognitive late effects are balanced, we explored the feasibility of neural stem cell sparing using VMAT. Whole brain irradiation with VMAT allows for beneficial neural stem cell sparing, although further studies are warranted to determine exactly what reduced stem cell dose levels are adequate to minimize downstream cognitive decline.

References

D. Roman, P. Sperduto; Neuropsychological effects of cranial radiation: current knowledge and future directions; Int J Radiat Oncol Biol Phys, 31(4); (1995), pp. 983-998

N. Broadbent, L. Squire, R. Clark; Spatial memory, recognition memory, and the hippocampus; Proc Natl Acad Sci, 101(40); (2004), pp. 14515-20

H. Hodges, N. Katzung, P. Sowinski, J. Hopewell, J. Wilkinson, T. Bywaters, M. Rezvani; Late behavioural and neuropathological effects of local brain irradiation in the rat; Behav Brain Res, 91; (1998), pp. 99–114

I. Barani, L. Cuttino, S. Benedict, D. Todor, E. Bump, Y. Wu, T. Chung, W. Broaddus, P. Lin; Neural Stem Cell-Preserving External-Beam Radiotherapy of Central Nervous System Malignancies; Int J Radiat Oncol Biol Phys, 68(4); (2007), pp. 978-985