Analysis of Serial Changes in Perfusion Parameters for Patients with Recurrent High Grade Gliomas being Treated with Radiosurgery

A. A. Chan[1], A. Pirzkall[2], S. J. Nelson[1]

[1]Department of Radiology, University of California, San Francisco, CA, United States, [2]Department of Radiation Oncology, University of California, San Francisco, CA, United States

Introduction

Radiation causes damage to endothelial cells and produces changes in the microvasculature such as occlusion of blood vessels, increased permeability of capillaries, and complete collapse of the blood-brain barrier (BBB) [1-2]. Given the high dose of radiation used in treating malignant gliomas with radiosurgery, changes in tumor and, to some degree, surrounding normal tissue are expected to occur. Dynamic susceptibility contrast (DSC) imaging can provide several perfusion parameters that can be used to monitor therapy. Because these parameters are based on functional changes that may occur prior to anatomical changes, they are expected to reveal early information about the tumor microenvironment and aid in monitoring response to therapy. Cerebral blood volume and peak height are two parameters that provide information about the density and architecture of blood vessels (or lack thereof) via signal changes that occur as a bolus of contrast agent passes through. Leakage during the recirculation phase provides information about the amount of contrast that has extravasated and is related to the permeability of local blood vessels. This preliminary study assesses the changes of these perfusion parameters within the radiosurgical target and surrounding tissue.

Methods

Nine patients with recurrent high grade gliomas (1 Grade III/8 Grade IV; 6M/3F; age range = 32-81 years old, median age = 46 years) were treated with Gamma Knife (GK) radiosurgery. A dose of 14.5-18.5 Gy (median 16.5 Gy) was prescribed to the 50% isodose line (IDL) which is tailored to encompass the radiosurgical target, allowing the highest dose to accumulate within the target. An MRI/MRSI exam was performed within one week before treatment and follow-up (FU) exams were acquired every few months (range 1-7 FUs/patient, median 4 FUs/patient, cohort total 29 FUs; FU time range = 1.05-10.98 months, median FU time = 4.8 months). Exams were performed on a 1.5T Signa clinical scanner (GE Medical Systems, Milwaukee, WI). The imaging sequence included an axial post-Gd T1-weighted 3D spoiled gradient echo (SPGR) image (TR/TE = 32/8 ms; flip θ = 40°; matrix = 256x256, FOV = 240x240 mm, slice thickness = 1.5 mm). DSC images were acquired using an echo-planar spin-echo sequence (TR/TE = 1700/100 ms; 256x256 matrix, FOV = 400x400 mm; slice thickness = 6.0 mm; 50 acquisitions; 0.2 mmol/kg administered with a power injector).

Data sets were sent to a SUN workstation for post-processing utilizing in-house programs. DSC images from follow-up exams were aligned to the pre-GK exam [3]. All DSC images were downsampled to an in-plane resolution of 5x5 mm and the dose distribution map was subsequently resampled to match the DSC images. Signal-time curves, $S(t)$, were created for each voxel and converted to concentration-time curves using the equation $C(t) = k \cdot \ln[S(0)/S(t)]/TE$. To minimize contamination due to recirculation and leakage effects, theoretical first-pass concentration-time curves, $C_{fp}(t)$, were produced by robustly fitting a simplified gamma-variate function to $C(t)$ [4]. Relative cerebral blood volume (rCBV) and peak height (rPH) were calculated as the area under $C_{fp}(t)$ and the maximum of $C_{fp}(t)$, respectively. Both parameters were normalized so that normal white matter (WM) equated 100. Relative leakage (rL) was calculated by subtracting $C_{fp}(t)$ from $C(t)$, integrating the resulting curve from the bolus end to 20 time-points after, and dividing that value by rCBV for normalization. Note that this phase of the curve also conveys information about recirculation [5], but since T1 relaxivity effects dominate, signal changes are primarily due to leakage. Figure 1 depicts the perfusion parameters derived from $C_{fp}(t)$ and $C(t)$.

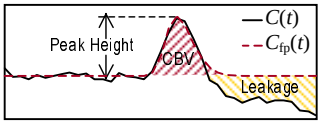

Figure 1. Typical measured and first-pass concentration-time curves with perfusion parameters denoted.

Voxels were classified into three classes depending on the dose received (0-25%, 25-50%, and ≥ 50% max dose) and then grouped into their respective time-points. For each class and time-point, the median values of the perfusion parameters were calculated. The values from follow-up exams were compared to pre-GK values by using the Kruskal-Wallis test, which is the nonparametric analogue of the one-way analysis of variance for numerous groups. Differences between the mean ranks of time-point groups were considered to be statistically significant when $P<0.05$. Curve fitting and statistical analysis were completed using MATLAB.

Results

Table 1 lists the median values of the perfusion parameters within the various dose classes. Values in bold are significantly different from their corresponding pre-GK value. For voxels that were within the 25% IDL (25-50% and ≥ 50% of max dose), both rCBV and rPH decrease with time and at six months after treatment, reaching 59% to 70% of their pre-GK values. rPH for voxels that were within the 50% IDL (≥ 50% of max dose) exhibits the greatest decrease, dropping to 59% of its pre-GK value. For voxels that were within the 50% IDL, rL experiences a significant increase 2-4 months after GK and then a trending decrease after six months. Figure 2 contains graphical representations of the serial changes for each of the perfusion parameters.

		Time Post-GK [months]				
	Max Dose	Pre	0-2	2-4	4-6	6+
rCBV	0-25%	101.4	100.7	102.8	102.2	101.8
	25-50%	75.6	69.8	**56.0**	**57.4**	**52.4**
	≥ 50%	51.7	49.0	**35.6**	**35.1**	**34.5**
rPH	0-25%	101.7	100.7	102.6	102.8	101.9
	25-50%	73.5	71.3	**59.5**	**58.1**	**51.1**
	≥ 50%	50.0	55.9	**31.5**	**35.5**	**29.7**
rL	0-25%	-3.3	-4.0	-2.7	-2.6	-3.3
	25-50%	-0.4	1.5	**3.0**	**4.7**	**2.1**
	≥ 50%	7.3	**15.3**	**22.1**	**21.7**	7.8

Table 1. Median values of perfusion parameters.

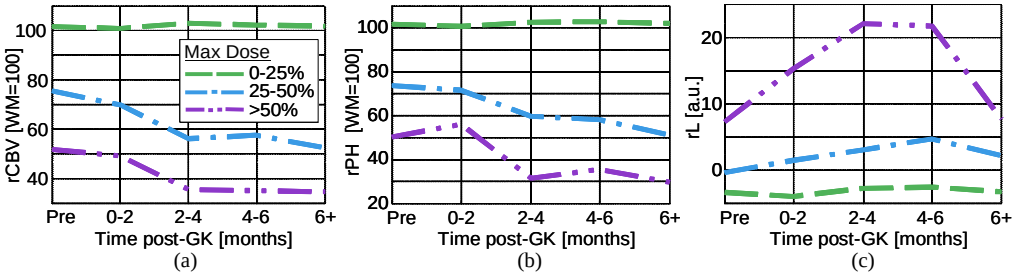

Figure 2. Serial time course of (a) rCBV, (b) rPH, and (c) rL for voxels receiving low- (– –), moderate- (– · –) and high-doses (– · · –).

Discussion

The decrease in rCBV and rPH for high-dose voxels indicates the development of radiation necrosis, a late delayed effect of radiation response and the ultimate goal of radiosurgical treatment to the outlined target. If we assume that rPH is a more sensitive measure compared to rCBV (since it is less prone to fitting errors that occur near the bolus end), the larger drop in peak height for high-dose voxels suggests a possible dose dependency or altered microvasculature within the target. The transient increase of rL in the target is likely a radiation effect causing a temporary hyperpermeability of blood vessels. The drop in rL after six months suggests that the BBB partially recovers. There may be transient changes in contrast enhancement 2 to 6 months after therapy that are oftentimes confused with tumor recurrence. Future work will relate changes in perfusion parameters to clinical outcome and compare the information provided by DSC with the observed changes in metabolic abnormalities as defined by *in vivo* MR spectroscopy. This will help to identify patterns of radiation necrosis and tumor recurrence early on and may elucidate the clinical role of perfusion-weighted imaging.

References

1. Trnovec T, et al, *Int J Rad Onc Biol Phys* 19:1581-1587 (1990). **2.** Van Vulpen M, el. al., *Onc Reports* 9:683-688 (2002). **3.** Woods RP, et al, *J Comp Assist Tomog* 22:139-152 (1998). **4.** Madsen MT. *Phys Med Biol* 37:1597-1600 (1992). **5.** Kassner A, et al, *J Magn Reson Imag* 11:103-113 (2000).

Acknowledgments

This research was supported by grants NIH RO1 CA59880 and NIGMS R25 GM56847.