Relating Physiological MR Imaging to Neurocognitive Function in Patients with Glioma

Janine M Lupo[1], Caroline A Racine[2], Angela Jakary[1], Sarah J Nelson[1,3], Susan M Chang[2], and Nicholas Butowski[2]

[1]*Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, United States,* [2]*Department of Neurological Surgery, University of California, San Francisco, CA, United States,* [3]*Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, United States*

Introduction: Having objective means for integrating neurocognitive function into the management of patients with high-grade glioma (HGG) is becoming increasingly important as new treatments extend survival and the late effects of therapy become relevant. The current frameworks for understanding neurocognitive changes over time remain limited, and may benefit from correlation with imaging which may provide insight into the pathogenesis of treatment-related brain injury. The goals of this pilot study were 1) to identify quantitative physiological parameters obtained from diffusion-weighted, perfusion-weighted, and spectroscopic MR imaging prior to surgery and subsequent therapy that may relate to measured neurocognitive impairment; and 2) to explore whether the same parameters are related to cognitive changes after surgery (pre-radiation) and 6 months post-radiation.

Table 1: Neurocognitive test

DOMAIN	TEST
GLOBAL FUNCTION	MoCA
FINE MOTOR	Pegs: Dominant Hand
	Pegs: Nondominant Hand
PROC. SPEED	DKEFS Numbers
	SDMT-Written
	SDMT-Oral
ATTENTION	Digit Span FORWARD
	Vis Attn Time
	Vis Attn Errors
VERBAL MEMORY	List Learning
	Delayed List Recall
	Story Learning
	Delayed Story Recall
VISUAL MEMORY	Complex Figure Recall
VISUAL-SPATIAL	Object Discrimination
	Complex Figure Copy
LANGUAGE	Letter Fluency (FAS)
	Category Fluency (Animals)
	Object Naming (BNT)
EXECUTIVE Fx	DKEFS Number-Letter
	Digit Span BACKWARD
	Design Fluency % Accuracy

Methods: Fifteen patients with HGG who agreed to comprehensive neuropsychological assessment and MR imaging (13 grade IV, 2 grade III; median age: 51.5 years, range: 28-63 years), were prospectively recruited for this study. Nine of these patients were evaluated prior to surgical resection of their tumor (baseline) or any subsequent treatment. Eight patients were first assessed either immediately prior to (6/8) or two weeks after (2/8) receiving radiation therapy (3-4 weeks post-surgery) and then again at 6 months post-radiation. Patients were scanned on 3T GE systems equipped with 8-channel phased array head coils. The imaging exam consisted of T1-weighted and T2-weighted anatomical imaging, DSC perfusion-weighted imaging (PWI) (0.1mm/Kg gadolinium bolus injected at 5ml/s; TR/TE/flip = 1500ms/35ms/35°, 80 time points, 24 slices, 4mm slice thickness, 26cm FOV, 128x128 matrix, ASSET w/R=2), diffusion-weighted imaging (DWI) (b = 1000 s/mm^2, 6 gradient directions, 4 NEX, TR/TE = 7000/76ms, 128x128 matrix with 22cm FOV, ASSET w/R=2, 3mm slice thickness), and 3D lactate-edited H-1 MRSI (2-D phase encoding and 1-D flyback EPSI encoding, TR/TE=1000-1100/144ms, matrix size 16x16x16, 1cc). The above parameters were selected to achieve maximum supratentoral brain coverage in addition to the tumor site and the MRSI was acquired with automated PRESS volume and out of voxel saturation bands prescription for maximum brain coverage. Parameters quantified included median rCBV, peak height (PH), recirculation factor (RF), and percent recovery (%Rec) from the PWI; ADC, FA, longitudinal diffusivity (LD), and radial diffusivity (RD) from the DWI; and NAA and NAA/creatine from the MRSI. All values were normalized and calculated within both normal appearing white matter (NAWM) and the non-contrast-enhancing T2 lesion (NEL). Patients also underwent a comprehensive 90-minute neuro-psychological battery that was sensitive to deficits across a wide range of cognitive domains within the same week as the MRI exam. All raw neurocognitive scores were converted to z-scores using age-appropriate normative data and combined across the major domains listed in Table 1. Spearman Rank correlations were applied to test for correlations between neurocognitive indices and imaging parameters at different time points.

Table 2. Summary of significant correlations between imaging and neurocognitive indices at all time points

Time Point	*Ncog Domain*	*Imaging Parameter*	*Region*	*r - value*	*p - value*
Pre-surgery Baseline (N=9)	Global MoCA	rCBV (PWI)	NEL	0.76	0.036
	Fine Motor	ADC (DWI)	NEL	-0.70	0.043
	Verbal Memory	FA (DWI)	NEL	0.74	0.046
	All Combined	rCBV (PWI)	NEL	0.86	0.005
	Combined Memory	rCBV (PWI)	NAWM	0.72	0.052
	Visual	PH (PWI)	NAWM	0.91	0.005
RT (N=8)	Fine Motor	%Rec (PWI)	NEL	-0.83	0.009
	Processing Speed	%Rec (PWI)	NEL	-0.76	0.021
	Processing Speed	FA (DWI)	NEL	-0.72	0.037
	Visual Memory	%Rec (PWI)	NEL	-0.77	0.021
	Combined Memory	PH (PWI)	NEL	-0.68	0.050
	Visual-Spatial	PH (PWI)	NEL	-0.82	0.011
	Visual-Spatial	rCBV (PWI)	NEL	-0.83	0.008
	Executive Fx	rCBV (PWI)	NEL	-0.74	0.028
	All Combined	rCBV (PWI)	NEL	-0.73	0.032
	Executive Fx	%Rec (PWI)	NAWM	-0.73	0.032
	All Combined	%Rec (PWI)	NAWM	-0.85	0.005
	Global MoCA	NAA (MRSI)	NAWM	-0.68	0.053
	Processing Speed	%Rec (PWI)	NAWM	-0.72	0.034
	Verbal Memory	%Rec (PWI)	NAWM	-0.70	0.040
	Visual Memory	%Rec (PWI)	NAWM	-0.90	0.002
	Combined Memory	%Rec (PWI)	NAWM	-0.82	0.011
	Visual	%Rec (PWI)	NAWM	-0.73	0.031
6m follow-up (N=8)	Global MoCA	RF (PWI)	NEL	0.85	0.012
	Fine Motor	rCBV (PWI)	NEL	-0.77	0.051
	Verbal Memory	RF (PWI)	NEL	0.83	0.017
	Combined Memory	RF (PWI)	NEL	0.92	0.003
	Language	RF (PWI)	NEL	0.96	0.001
	All Combined	RF (PWI)	NEL	0.95	0.001
	Global MoCA	rCBV (PWI)	NAWM	0.72	0.052
	Processing Speed	RF (PWI)	NAWM	0.73	0.048
	Attention	ADC (DWI)	NAWM	-0.76	0.037
	Attention	FA (DWI)	NAWM	0.79	0.028
	Attention	RD (DWI)	NAWM	-0.78	0.030
	Visual Memory	PH (PWI)	NAWM	0.91	0.005
	Visual Memory	%Rec (PWI)	NAWM	-0.86	0.012
	Visual Memory	rCBV (PWI)	NAWM	0.96	0.001
	Visual Memory	RF (PWI)	NAWM	0.75	0.038
	Combined Memory	PH (PWI)	NAWM	0.73	0.046
	Combined Memory	rCBV (PWI)	NAWM	0.87	0.009
	All Combined	rCBV (PWI)	NAWM	0.80	0.024

Results & Discussion: Table 2 displays all the significant correlations between imaging parameters and neurocognitive indices. Perfusion parameters were most often associated with cognitive measures at all time points, especially relating vessel leakiness with memory. Diffusion parameters were mostly associated with attention at 6 months. Of the parameters considered, NAA was the least frequently associated with any neurocognitive function. Although prior to surgery more associations were found within the NEL region, with neurocognitive deficits caused mostly by the tumor, over time, more correlations occurred within the NAWM region, suggesting that therapy affected cognitive measures.

Conclusions: This pilot study demonstrates a framework from which to implement multi-modality MR imaging to assess neurocognitive function that has the potential to assess and track longer-term effects of therapy on cognition and provide insight into the biological basis for the neurocognitive deficits observed. Future studies will explore the relationship between the magnitude of decline in each neurocognitive domain and specific regional changes in imaging parameters, including the evaluation of how white matter fiber integrity within specific fiber tracks from DTI relates to decline in associated neurocognitive function, and investigate whether imaging metrics before therapy can determine neurocognitive outcome.

This research was supported by a brain tumor SPORE career development award under the NIH grant P50 CA97257