A Prospective Cohort Study of Neural Progenitor Cell-Sparing Radiation Therapy Plus Temozolomide for Newly Diagnosed Patients With Glioblastoma

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BACKGROUND: In treating glioblastoma, irradiation of the neural progenitor cell (NPC) niches is controversial. Lower hippocampal doses may limit neurocognitive toxicity, but higher doses to the subventricular zones (SVZ) may improve survival.

OBJECTIVE: To prospectively evaluate the impact of limiting radiation dose to the NPC niches on tumor progression, survival, and cognition in patients with glioblastoma.

METHODS: Patients with glioblastoma received resection followed by standard chemoradiation. Radiation dose to the NPC niches, including the bilateral hippocampi and SVZ, was minimized without compromising tumor coverage. The primary outcome was tumor progression in the spared NPC niches. Follow-up magnetic resonance imaging was obtained bimonthly. Neurocognitive testing was performed before treatment and at 6- and 12-mo follow-up. Cox regression evaluated predictors of overall and progression-free survival. Linear regression evaluated predictors of neurocognitive decline.

RESULTS: A total of 30 patients enrolled prospectively. The median age was 58 yr. Median mean doses to the hippocampi and SVZ were 49.1 and 41.8 gray (Gy) ipsilaterally, and 16.5 and 19.9 Gy contralaterally. Median times to death and tumor progression were 16.0 and 7.6 mo, and were not significantly different compared to a matched historical control. No patients experienced tumor progression in the spared NPC-containing regions. Overall survival was associated with neurocognitive function ($P \leq .03$) but not dose to the NPC niches. Higher doses to the hippocampi and SVZ predicted greater decline in verbal memory ($P \leq .01$).

CONCLUSION: In treating glioblastoma, limiting dose to the NPC niches may reduce cognitive toxicity while maintaining clinical outcomes. Further studies are needed to confirm these results.

KEY WORDS: Glioblastoma, Neural progenitor cells, Neurocognitive outcomes, Overall survival, Tumor control

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In the treatment of glioblastoma, the standard of care is resection followed by chemoradiation.[1,2] While strategies to improve survival and delay tumor progression remain the highest priority, improved preservation of neurocognitive function is necessary as long-term survival increases.

While a relationship between tumor control and preservation of neurocognitive function is well established,[3-6] the role of the neural progenitor cell (NPC) niches remains controversial. NPC, found in the subventricular zones (SVZ) of the lateral ventricles and the hippocampal dentate gyri, produce new

ABBREVIATIONS: CI, confidence interval; **COWA,** Controlled Oral Word Association; **CTV,** clinical target volume; **CT,** computed tomography; **FLAIR,** fluid-attenuated inversion recovery; **Gy,** gray; **GTV,** gross tumor volume; **HVLT-R,** Hopkins Verbal Learning Test-Revised; **KPS,** Karnofsky Performance Status; **MRI,** magnetic resonance imaging; **NPC,** neural progenitor cell; **OS,** overall survival; **PTV,** planning target volume; **PFS,** progression-free survival; **RT,** radiation therapy; **RDI,** Recognition Discrimination Index; **SVZ,** subventricular zone

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neurons and glia through adulthood[7-9] and may aid in repair after injury.[10,11] Preclinical evidence suggests that irradiation of the NPC niches may pose a conflict between minimizing cognitive decline and maximizing survival. While irradiating the NPC niches leads to death of proliferating cells[12] and neurocognitive decline in rodents,[13-15] NPC may also be involved in the development of glioblastoma.[16,17] This conflict is reflected in the clinical literature. While several recent studies suggest that increased dose to the SVZ may improve survival or tumor control in patients with glioblastoma,[18-20] these findings are debated.[21] Simultaneously, the relationship between hippocampal irradiation and cognitive decline[22-27] suggests a functional role of NPC niches.

This study represents the first prospective evaluation of overall survival (OS), progression-free survival (PFS), and neurocognitive changes in patients with newly diagnosed glioblastoma, following radiation therapy (RT) designed to spare excess dose to the NPC niches without compromising coverage of the target volume.[28] The a priori hypothesis was that this NPC-sparing strategy may allow tumor control and survival consistent with the standard of care, while mitigating treatment-induced neurocognitive decline. The findings of this study support this hypothesis. OS and PFS were comparable to a historical control, and recurrence in the spared NPC niches was not observed. Furthermore, lower radiation doses to the NPC niches were associated with less severe deterioration of verbal memory, suggesting that NPC-sparing RT may aid in preserving cognition.

METHODS

Patient Selection

This single-arm prospective cohort study accrued patients at a single institution from December 2011 to January 2014. Patients were followed until 24 mo after RT or death. Adults with histologically diagnosed glioblastoma within 12 wk of any extent of resection (gross total, subtotal, or biopsy only) and a Karnofsky Performance Status (KPS) score $\geq$ 60 prior to treatment were eligible. Patients with prior malignancies or cranial irradiation were excluded. Institutional Review Board approval was obtained. Enrolled patients provided written consent for their participation. Clinical Trials registration number: NCT01478854.

Treatment

Patients received intensity-modulated RT totaling 60 gray (Gy) in 30 fractions, with concurrent and adjuvant temozolomide. The initial gross tumor volume (GTV) was defined by the hyperintense region on gadolinium-enhanced T1 magnetic resonance imaging (MRI), contrast-enhanced computed tomography (CT), and T2 fluid-attenuated inversion recovery (FLAIR) MRI. The clinical target volume (CTV) was defined as the GTV plus a 0.5- to 0.7-cm uniform margin. The planning target volume (PTV) was defined as the CTV plus a 0.5-cm margin. This initial PTV was treated with 46 Gy. The cone-down PTV, which received the final 14 Gy, was defined by the hyperintense region on gadolinium-enhanced T1 MRI and contrast-enhanced CT, with the same CTV and PTV expansions described above.

The NPC niches, consisting of the bilateral hippocampi and SVZ, were delineated as avoidance structures (Figure 1). The SVZ avoidance structure was defined as a 0.5-cm uniform margin adjacent to the lateral wall of the lateral ventricle. The hippocampus avoidance structure was defined as the hippocampus plus a 0.5-cm uniform expansion. To guarantee adequate PTV coverage, no attempt was made to spare the NPC niches within a 2-cm margin of the PTV. Dose to the NPC niches outside this 2-cm margin was reduced as much as possible, while meeting other normal tissue constraints and without compromising coverage of the PTV.[28] Thus, prespecified dose constraints were not defined for the hippocampi and SVZ; the potential for dose sparing was ultimately determined by tumor geometry and location relative to the NPC niches.

The scheduled temozolomide regimen consisted of 75 mg/m^2/d, 7 d per week from the first to the last day of RT, followed by 150 to 200 mg/m^2/d for 5 d during each 28-d cycle for 6 cycles. Temozolomide could be discontinued or modified by the treating medical oncologist. Patients were not permitted any therapeutic agents besides temozolomide to treat their glioblastoma, until tumor progression or 1-yr follow-up.

Primary Endpoint and Sample Size

The primary endpoint was tumor progression within the spared NPC-containing regions, 1 yr after RT. Tumor progression was identified on gadolinium-enhanced T1 and T2 FLAIR MRI. MRI surveillance was performed at 1 mo after RT and bimonthly thereafter. The rate of tumor progression within the spared regions was hypothesized to be $\leq$25%, based on the investigators' consensus that 25% treatment failure was the upper limit of clinical acceptability. Using an empirical entropy-based approach,[29] a sample size of 30 patients was determined to have the optimal information gain (relative certainty).

Additional Oncological and Neurocognitive Outcomes

Tumor progression was classified as out-of-field, in-field, or marginal. Cases were considered out-of-field if one or more foci of recurrent tumor were entirely located >2 cm beyond the PTV. Remaining cases of recurrence were considered in-field or marginal, respectively, if >95% or <95% of the recurrent tumor overlapped with the PTV.

Neurocognitive testing was performed by a neuropsychologist before treatment and at 6 and 12 mo after RT, with instruments outlined in **Supplemental Digital Content 1**. Processing speed was evaluated using the Coding subset of the Wechsler Adult Intelligence Scale-Fourth Edition (Coding)[30] and Trail Making Test (Trails A).[31,32] Executive function was evaluated using the Trail Making Test (Trails B)[31,32] and Controlled Oral Word Association test (COWA).[33] Verbal learning and memory were evaluated using the Hopkins Verbal Learning Test-Revised (HVLT-R), comprising the following components: Total Recall, Delayed Recall, Percent Retained, and Recognition Discrimination Index (RDI).[34]

Statistical Methods

Neurocognitive outcomes were assessed as the change in raw score compared to baseline. Outcomes obtained after tumor progression were disregarded.

OS and PFS functions were estimated using the Kaplan-Meier modeling. Patients lost to follow-up were censored at the date of their

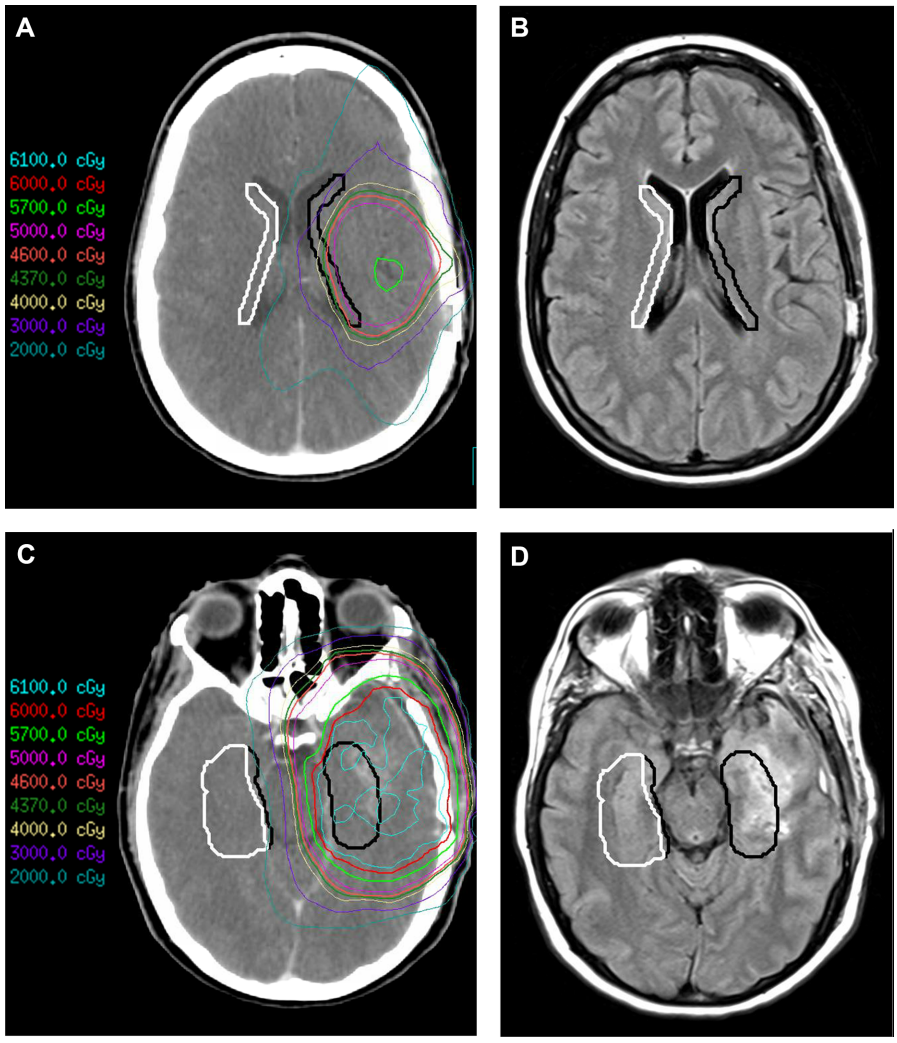

FIGURE 1. *Sample treatment plan with NPC niches delineated. Representative images are obtained from CT* **A** *and* **C** *and T2 FLAIR MRI* **B** *and* **D**. *Radiation isodose lines are shown on CT. NPC niches (subventricular zones and hippocampi) are identified with thick outlines. A superior slice* **A** *and* **B** *shows the subventricular zones, and an inferior slice shows the hippocampi* **C** *and* **D**. *Note that in order to achieve full coverage of the left temporal tumor, only part of the NPC niches were spared (shown in white), whereas no attempt was made to spare the NPC niches within 2 cm of the PTV (shown in black).*

last clinical visit, for evaluation of OS, and the date of their last brain MRI, for evaluation of PFS.

A matched cohort analysis was performed to compare OS and PFS between the prospective cohort treated with NPC-sparing RT and a historical control cohort of patients with glioblastoma treated with standard RT at the same institution. This historical cohort was previously described in a retrospective analysis.[20] Patients in the prospective and historical control cohorts were matched in a 1:2 ratio, respectively, by age (within 15 yr), KPS score (within 15), extent of resection (gross total vs subtotal), and GTV (within 50 mL).

Univariate Cox regression evaluated predictors of OS and PFS. Multivariate Cox regression assessed whether dose to the NPC niches or neurocognitive changes predicted OS and PFS. Potential covariates included age, sex, education (> or ≤12 yr), gross tumor characteristics (volume, location, extent of resection), MGMT methylation status, and dose to the uninvolved whole brain parenchyma. Initial multivariate models included all potential covariates. Final parsimonious models were produced by removing the covariates that contributed least to the overall model quality, assessed by the Akaike information criterion. Given the size of the cohort, final models were each limited to a maximum of 2 covariates.

Multivariate linear regression evaluated whether dose to the NPC niches predicted neurocognitive decline. The same set of potential covariates was considered, excluding MGMT methylation status.

TABLE 1. Patient, Tumor, and Treatment Characteristics

Characteristic		Median (range) or number (%)
Age (yr)		58 (35-87)
Sex (female)		14 (46.7%)
Education	Number of years	16 (8-22)
	> 12 years	20 (66.7%)
Karnofsky performance status (KPS) score during first week of radiation therapy		90 (70-100)
Mini-mental state exam, prior to treatment		26 (0-30)
Tumor location	Frontal	9 (30%)
	Parietal	11 (36.7%)
	Temporal	17 (56.7%)
	Occipital	6 (20%)
Tumor size (cc)		76.9 (12.0-277.7)
Tumor extension across midline		1 (3.3%)
Resection extent	Gross total	17 (56.7%)
	Subtotal	13 (43.3%)
MGMT promoter methylation	Positive	8 (26.7%)
	Negative	14 (46.7%)
	Unknown	8 (26.7%)
Mean dose to hippocampus (Gy)	Ipsilateral	49.1 (0.9-61.4)
	Contralateral	16.5 (0.9-35.8)
	Bilateral	34.7 (0.9-48.2)
Mean dose to SVZ (Gy)	Ipsilateral	41.8 (6.1-59.7)
	Contralateral	19.9 (4.4-53.6)
	Bilateral	31.0 (6.0-54.8)
Mean dose to whole brain, excluding the GTV (Gy)		26.4 (11.8-39.3)
Adjuvant temozolomide cycles delivered		5 (0-6)
Tumor progression		26 (86.7%)
Location of progression	In field	21 (80.8%)
	Marginal	4 (15.4%)
	Out of field	1 (3.8%)

TABLE 2. Neurocognitive Measures at Baseline and 6-Month Follow-up

Neurocognitive measure	Time point	Mean (95% CI)	Patients evaluated
Coding	Baseline	55.4 (46.4-64.4)	29
	Follow-up	46.1 (29.9-62.2)	14
	Change	−6.9 (−12.9 to −0.8)	14
Trails A	Baseline	58 (37.8-78.2)	28
	Follow-up	72.3 (18.1-126.4)	13
	Change	20.6 (−21.4 to 62.6)	12
Trails B	Baseline	146.2 (93.3-199.1)	27
	Follow-up	120.3 (63.4-177.2)	13
	Change	−14.7 (−59.8 to 30.5)	12
COWA	Baseline	28.5 (23.3-33.6)	29
	Follow-up	31.4 (21.5-41.2)	14
	Change	2.6 (−2.8 to 8.1)	14
HVLT-R Total Recall	Baseline	20.5 (18-23)	30
	Follow-up	20.6 (15.1-26.2)	14
	Change	−1.4 (−4.1 to 1.3)	14
HVLT-R Delayed Recall	Baseline	6.3 (5-7.6)	30
	Follow-up	6.9 (4.3-9.5)	14
	Change	−0.6 (−2.4 to 1.1)	14
HVLT-R Percent Retained	Baseline	69 (56.1 to 81.9)	30
	Follow-up	70 (46.3 to 93.8)	14
	Change	−10.6 (−27.9 to 6.7)	14
HVLT-R Recognition Discrimination Index	Baseline	9.9 (9-10.8)	29
	Follow-up	9.9 (8.6-11.2)	14
	Change	−0.3 (−1.4 to 0.8)	14

Initial and final multivariate models were produced as described above.

$P < .05$ was considered statistically significant. Statistical analyses were performed in R version 3.4.4 (R Foundation for Statistical Computing).[35]

RESULTS

Baseline Characteristics and Changes in Neurocognitive Function

A total of 30 patients with newly diagnosed glioblastoma enrolled in this prospective study (Table 1). The cohort included 14 females (46.7%) and 16 males (53.3%). The median age at the start of RT was 58 yr (range 35-87). A total of 20 patients (66.7%) had >12 yr of education. Eight patients (26.7%) had tumors with known MGMT promoter methylation. IDH1 immunostaining was negative in 19 cases (63%) and not performed in the remainder. Resection was gross total in 17 cases (56.7%) and subtotal in 13 cases (43.3%). The medians of the mean doses to the ipsilateral and contralateral hippocampi were 49.1 Gy (range 0.9-61.4) and 16.5 Gy (range 0.9-35.8). The medians of the mean doses to the ipsilateral and contralateral SVZ were 41.8 Gy (range 6.1-59.7) and 19.9 Gy (range 4.4-53.6). Dose to the bilateral hippocampi was correlated with dose to the bilateral SVZ ($P = .0006$), but neither was significantly correlated with whole brain dose ($P > .05$).

Neurocognitive outcomes at baseline and 6-mo follow-up are reported (Table 2). Outcomes at 12-mo follow-up were used in place of outcomes at 6-mo follow-up for 3 patients not evaluated at 6 mo. A decline in mean processing speed (Coding, Trails A) and verbal learning and memory (HVLT-R) was observed from baseline to follow-up.

OS and PFS After NPC-Sparing RT Are Comparable to Standard RT

At the time of analysis, all but 3 patients (90%) died, and all but 4 patients (86.7%) experienced tumor progression. Median times to death and progression were 16.0 mo (95% CI 13.0-32.1) and

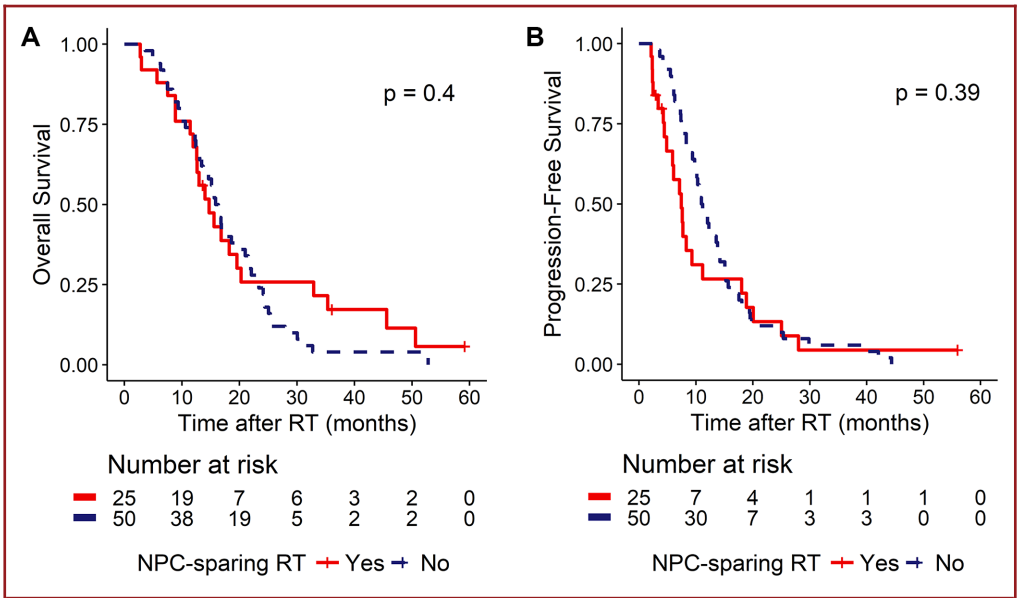

FIGURE 2. *A matched cohort analysis suggests that overall and progression-free survival after NPC-sparing radiation therapy are comparable to standard radiation therapy. Median time to death was 14.7 mo (95% CI 12.6-32.9) for the prospective cohort treated with NPC-sparing radiation therapy, compared to 16.1 months (95% CI 13.4-21.5) for the historical control group treated with standard radiation therapy (P = .40)* **A**. *Median time to tumor progression was 7.4 mo (95% CI 4.8-18.0) for the prospective cohort, compared to 11.0 mo (95% CI 9.8-14.1) for the historical control (P = .39)* **B**.

7.6 mo (95% CI 5.9-15.4), respectively. The median follow-up time was 36.1 mo among patients alive at the latest follow-up.

A matched cohort analysis compared outcomes between the prospective cohort treated with NPC-sparing RT and a historical control cohort treated with standard RT. A total of 25 patients from the prospective cohort were matched with 50 patients from the historical control cohort. No significant differences were observed in any of the variables used in matching ($P \geq .2$) (**Table, Supplemental Digital Content 2**). Among matched patients treated with NPC-sparing RT, the median of the mean doses to the contralateral SVZ was 9.1 Gy lower ($P = .0002$), and median of the mean doses to the bilateral SVZ was 7.0 Gy lower ($P = .003$), compared to matched patients treated with standard RT. Hippocampal doses were not measured in the historical control cohort. OS and PFS did not differ significantly between the matched cohorts ($P = .40$, $P = .39$), (Figure 2A and 2B).

Tumor Progression Did Not Occur in the Spared NPC Niches

Tumor progression was in-field, marginal, and out-of-field in 21 (81%), 4 (15%), and 1 case (4%), respectively. In all cases, the PTV directly overlapped with at least one of the NPC niches. Consequently, dose-sparing was limited to a subvolume of the NPC niches 2 cm or further from the PTV. On gadolinium-enhanced T1 MRI, no patients experienced tumor recurrence within these spared regions. On T2 FLAIR MRI, 1 patient had increased hyperintensity overlapping with the posterior-most aspect (<1 cc) of the contralateral SVZ, within the region of dose-sparing. However, gadolinium-enhanced T1 MRI did not indicate recurrent tumor.

OS and PFS Were Not Correlated With Radiation Dose to the NPC Niches

On univariate survival analysis, poorer OS and PFS were associated with lack of MGMT methylation ($P = .003$, $P = .006$), higher whole brain dose ($P = .01$, $P = .04$), and more advanced age ($P = .03$, $P = .049$) (Table 3). Furthermore, poorer OS was associated with greater decline in processing speed (Coding, $P = .004$; Trails A, $P = .03$) and verbal learning (HVLT-R Total Recall, $P = .02$) (Table 3). OS and PFS were not significantly correlated with mean dose to any of the NPC niches, including the ipsilateral, contralateral, and bilateral hippocampi and SVZ ($P > .05$).

On multivariate survival analysis, decline in verbal learning and processing speed were not independent predictors of OS ($P > .05$) when controlling for MGMT methylation status and whole brain dose. No significant correlation between dose to any of the NPC niches and either OS or PFS was detected when controlling for any combination of potential covariates ($P > .05$).

Higher Radiation Doses to the NPC Niches Are Associated With Greater Cognitive Decline

On multivariate linear regression, higher radiation dose to the NPC niches was independently associated with greater decline

TABLE 3. Significant Predictors of Overall and Progression-Free Survival

Outcome	Predictor	Hazard ratio	95% CI	*P* value
Overall survival	MGMT methylation	0.15	0.04-0.52	.003
	Dose to the whole brain	1.1/Gy	1.02-1.19	.01
	Age	1.04/yr	1.003-1.07	.03
	Change in processing speed (coding)	0.83	0.73-0.94	.003
	Change processing speed (Trails A)	1.02	1.002-1.03	.03
	Change in verbal learning (HVLT-R Total Recall)	0.80	0.66-0.97	.02
Progression-free survival	MGMT methylation	0.16	0.04-0.59	.006
	Dose to the whole brain	1.07/Gy	1.002-1.14	.04
	Age	1.03/yr	1.000-1.06	.049

Hazard ratios, 95% CIs, and p-values are obtained from univariate Cox regression.

in verbal memory but no other domains of neurocognitive function. Representative correlations are presented (Table 4, Figure 3), and a complete list of significant correlations is also provided (**Table** and **Figure**, **Supplemental Digital Content 3** and **4**). The neurocognitive measure most closely associated with dose to the NPC niches was HVLT-R Delayed Recall. Higher doses to the ipsilateral and bilateral hippocampi and SVZ each predicted greater decline in HVLT-R Delayed Recall, independent of education and whole brain dose ($R^2 \geq 0.78$, $P \leq .01$) (Table 4, Figure 3). The strongest correlation was between HVLT-R Delayed Recall and dose to the bilateral SVZ ($R^2 = 0.90$, $P = .0007$) (Table 4). This correlation remained significant when controlling for dose to the bilateral hippocampi in place of whole brain dose. HVLT-R Percent Retained and RDI were also associated with dose to the NPC niches (**Table** and **Figure**, **Supplemental Digital Content 3** and **4**).

Impact of Tumor Characteristics on Oncological and Neurocognitive Outcomes

When evaluating dose to the NPC niches as predictors of oncological and neurocognitive outcomes, anatomic tumor characteristics including GTV, extent of resection, temporal lobe involvement, and extension across the midline represent potential confounding factors and require further evaluation.

On univariate analysis, OS and PFS were not associated with GTV ($P \geq .4$), nor with gross total vs subtotal extent of resection ($P > .2$). These observations are consistent with the historical control cohort.[20] Furthermore, substituting GTV or extent of resection in place of other covariates within multivariate models of OS and PFS did not enhance the models' quality. GTV was associated with mean dose to the contralateral SVZ ($\beta = 8.8$ Gy/dL, $P = .007$), suggesting that greater tumor burden may partially explain high contralateral doses in some patients. However, differences in GTV do not directly explain differences in outcomes.

On univariate analysis, GTV, extent of resection, and temporal lobe involvement did not significantly predict change in verbal memory or other neurocognitive domains ($P > .05$).

TABLE 4. Higher Doses to the NPC Niches Are Associated With Greater Decline in Verbal Memory

Outcome	Predictor	β	*P* value (predictor)	R^2	*P* value (model)	Covariates
Change in HVLT-R Delayed Recall (baseline to 6-mo follow-up)	Mean dose to ipsilateral hippocampus	−0.064/Gy	.04	0.78	.01	Education > 12 yr ($\beta = 3.39$, $P = .01$) Dose to whole brain ($\beta = -0.13$/Gy, $P = .07$)
	Mean dose to bilateral hippocampi	−0.084/Gy	.03	0.78	.009	Education > 12 yr ($\beta = 3.12$, $P = .01$) Dose to whole brain ($\beta = -0.12$/Gy, $P = .07$)
	Mean dose to ipsilateral SVZ	−0.089/Gy	.003	0.89	.001	Education > 12 yr ($\beta = 4.60$, $P = .0004$) Dose to whole brain ($P = .7$)
	Mean dose to bilateral SVZ	−0.13/Gy	.0019	0.90	.0007	Education > 12 yr ($\beta = 4.74$, $P = .0002$) Dose to the whole brain ($P = .7$)

Representative outcomes of multivariate linear regression correlating dose to the NPC niches and decline in verbal memory from baseline to 6-mo follow-up are shown below. A complete list of significant correlations is presented in **Table**, **Supplemental Digital Content 3** and **Figure**, **Supplemental Digital Content 4**. Several characteristics of the patient, treatment, and disease were considered as potential covariates, but final parsimonious models were each limited to a maximum of 2 covariates. Model selection was performed by assessing the Akaike information criterion as a measure of relative model quality.

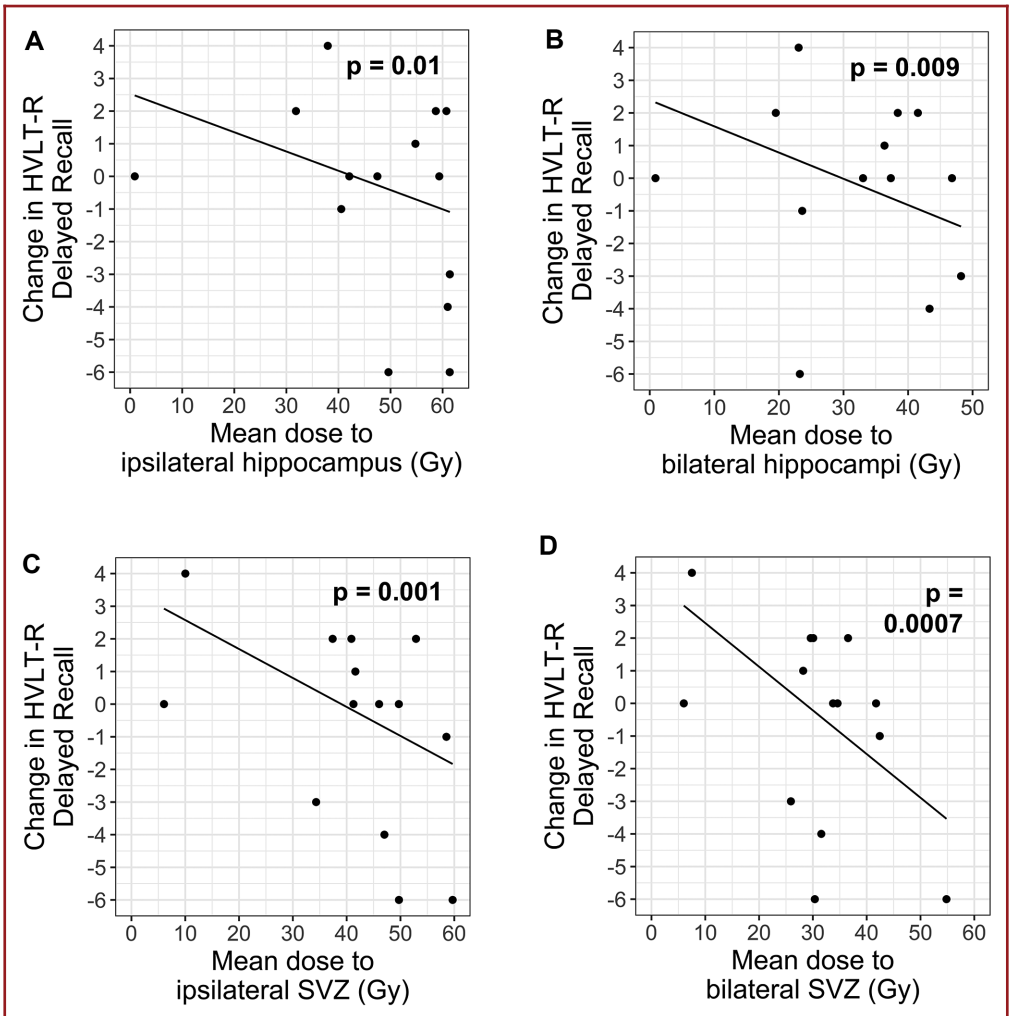

FIGURE 3. *Higher radiation doses to the NPC niches are associated with greater decline in verbal memory. Four representative correlations are shown here: dose to the ipsilateral hippocampus* **A**, *bilateral hippocampi* **B**, *ipsilateral SVZ* **C**, *and bilateral SVZ* **D** *vs decline in the Delayed Recall component of the Hopkins Verbal Learning Test-Revised. Additional correlations are presented in* ***Table***, ***Supplemental Digital Content 3*** *and* ***Figure***, ***Supplemental Digital Content 4***. *Lines of best fit are derived from outcomes of multivariate regression (Table 4); the slope was derived from the coefficient for the main predictor of interest, and the intercept was derived from the coefficients for the covariates.*

Furthermore, substituting GTV, extent of resection, or temporal lobe involvement in place of other covariates within multivariate models assessing change in HVLT-R Delayed Recall (Table 4) did not enhance the models' quality.

On contrast-enhanced T1 MRI, only 1 patient had gross tumor extension across the midline prior to RT. She experienced tumor progression at 2.3 mo and died at 8.8 mo after RT.

DISCUSSION

In the treatment of glioblastoma, the significance of irradiating the NPC niches remains controversial. Clinically, the controversy can be summarized as the potential to improve tumor control by irradiating NPC-containing regions vs the potential to preserve cognitive function by sparing them from excess dose. This prospective study investigated one approach to this dilemma: sparing excess dose to the NPC niches without compromising tumor coverage. This NPC-sparing strategy yielded OS and PFS similar to the standard of care. Simultaneously, lower doses to the NPC niches predicted for greater preservation of verbal memory, suggesting that this approach may also aid in protecting cognition. This novel strategy may improve quality of life of patients with glioblastoma and deserves further investigation in randomized trials.

The clinical course of glioblastoma is characterized by progressive neurocognitive deterioration. Verbal memory and executive function among newly diagnosed patients are significantly poorer compared to population norms,[36] and further decline in multiple neurocognitive domains is observed months after treatment.[3] In addition, neurocognitive decline in patients with glioblastoma is associated with mortality and tumor progression,[3-6] a finding that is reiterated in the current study.

From an anatomic perspective, higher radiation doses to the hippocampi and temporal lobes have been consistently correlated with neurocognitive decline, particularly in verbal memory. Multiple studies, including the current one, support this correlation,[22-27] while fewer studies did not detect a significant relationship between dose and measures of verbal memory.[37,38] Several randomized clinical trials, including NRG-CC001 and NRG-CC003, are underway to evaluate the effect of hippocampal-sparing RT.

Although no prior clinical studies demonstrate a relationship between irradiation of the SVZ and neurocognitive decline, preclinical evidence is consistent with such a relationship. NPC are especially sensitive to radiation,[39] and the SVZ constitute their largest reservoir in adulthood.[40] Animal studies report neurocognitive decline following irradiation of the NPC niches,[13-15] including a specific association between SVZ irradiation and long-term deficits in memory.[41] Additionally, cognitive deterioration after intrathecal chemotherapy may be explained by damage to the SVZ, given the low depth of penetration from within the ventricular system.[42,43] To our knowledge, the current study provides the first prospective clinical evidence of a potential correlation between dose to the SVZ and deterioration in verbal memory, which persisted when controlling for dose to the whole brain or bilateral hippocampi.

While reducing dose to the hippocampi or SVZ may aid in preserving cognition, the potential survival benefits of increased dose to the NPC niches must also be considered. Multiple studies have observed improved OS or PFS with greater SVZ dose in the treatment of glioblastoma.[18-20,44-49] However, details of this relationship, such as the importance of laterality and potential confounding factors, remain inconsistent. Ultimately, the current study does not address the question of whether higher radiation doses to the NPC niches may improve survival beyond the standard of care. This represents an important question under evaluation in an ongoing prospective trial (NCT02177578).

Our study does suggest that limiting dose to the NPC regions may not lead to poorer oncologic outcomes compared to the standard of care. Several findings support this hypothesis. First, OS and PFS reported in this study are comparable to a historical control,[20] as well as EORTC/NCIC 26981-22981.[1,2] Second, no cases of tumor progression were observed within the regions spared of extraneous dose. Third, there was no correlation between OS or PFS and dose to the NPC niches, despite a broad range of doses delivered (Table 1). Thus, the NPC-sparing strategy used in this study likely does not impinge on the efficacy of the standard of care in extending survival and delaying progression.

Limitations

The central limitations of this study are its sample size and compliance with neurocognitive testing. Although 30 enrolled patients were considered sufficient to estimate the risk of tumor progression in the spared NPC-containing regions, only 17 patients completed neurocognitive testing at 6- or 12-mo follow-up. Neurocognitive outcomes from 3 of these patients were obtained after tumor progression and were not analyzed. As 3 patients died and 13 patients experienced progression prior to 6-mo follow-up, declining functional status likely undermined compliance with neurocognitive testing. Furthermore, the diagnosis and treatment of glioblastoma place a substantial socioeconomic burden on patients and their families, and the time commitment required by serial neurocognitive testing must be weighed against competing demands. Ultimately, the sample size available for analysis is not statistically ideal but remains consistent with the nature of the disease and prior studies assessing neurocognitive function after intracranial irradiation.[3,4,26,27,36]

Separate from issues of sample size, MGMT methylation was not uniformly measured among the earliest patients accrued, and IDH1 mutation status was unknown for over a third of tumors. This is consistent with the time period in which the study was conducted. Additionally, this study does not include a detailed analysis of tumor location with respect to midline structures, which could further elucidate the anatomic correlates of cognitive deterioration. A detailed anatomic analysis should be pursued in future investigations. Future studies should also develop dose-response models to quantify the relationships between dose to the NPC niches and cognitive decline. Normal tissue complication probability models evaluating risk of memory deficits as a function of hippocampal dose have been presented by our group,[26] using a prospective cohort of 60 patients including those enrolled in the current trial. Similar modeling has not been performed for the SVZ and should be pursued using prospective data.

CONCLUSION

This is the first prospective study designed to evaluate the clinical and neurocognitive outcomes of radiation plans designed to spare dose to the NPC niches, while maintaining adequate tumor coverage, in patients with glioblastoma. This study suggests that NPC-sparing RT has the potential to provide similar OS and PFS compared to the standard of care, while potentially mitigating radiation-induced neurocognitive toxicity. Interestingly, this study is also the first to find that lower doses not only to the hippocampi but also to the SVZ may reduce deterioration of verbal memory. Nonetheless, this study is limited by its single-institution, single-arm design and small size. Consequently, its findings should be considered hypothesis-generating and not suitable for direct application in the clinic. Phase III, multi-institutional trials are needed to rigorously evaluate the benefits of NPC-sparing RT versus the standard of care.

Disclosures

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Supplemental Digital Content 1. Table. Measures of neurocognitive function. Characteristics of the instruments used to evaluate neurocognitive function in this study are summarized.

Supplemental Digital Content 2. Table. Pertinent patient, tumor, and treatment characteristics of the matched cohorts. To assess the impact of NPC-sparing radiation therapy, 25 patients in the prospective cohort treated with NPC-sparing were matched with 50 patients from a historical control cohort treated with standard radiation therapy.

Supplemental Digital Content 3. Table. Higher doses to the NPC niches are associated with greater decline in verbal memory. Significant outcomes of multivariate linear regression evaluating dose to the NPC niches as predictors of change in verbal memory from baseline to 6-mo follow-up are shown. Age, sex, education ($\leq$ or $>$ 12 yr), and dose to the whole brain were considered as potential covariates but final parsimonious models were each limited to a maximum of 2 covariates. Model selection was performed by assessing the Akaike information criterion as a measure of relative model quality.

Supplemental Digital Content 4. Figure. Higher doses to the NPC niches are associated with greater decline in verbal memory. The following plots show significant relationships between dose to the neural progenitor cell niches (subventricular zones and hippocampi) and decline in verbal memory, measured by components of the Hopkins Verbal Learning Test-Revised: Delayed Recall (**A**-**E**), Percent Retained (**F**-**G**), and Recognition Discrimination Index (**H**-**I**). Lines of best fit are derived from outcomes of multivariate regression (**Table, Supplemental Digital Content 3**); the slope was derived from the coefficient for the main predictor of interest, and the intercept was derived from the coefficients for the covariates.