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Radiation Dose and Volume Effects on Cognitive Function in Patients with Glioblastoma Multiforme (GBM) Treated with Radiation Therapy and Temozolomide

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Abstract

Background: Glioblastoma multiforme (GBM) is a highly aggressive brain tumor with a poor prognosis. Radiation therapy (RT) and temozolomide (TMZ) are standard treatments, but their impact on cognitive function is not well understood.
Objective: To investigate the effects of radiation dose and TMZ dose on cognitive function in patients with GBM treated with RT and TMZ.
Methods: This retrospective study included 162 patients with GBM treated with RT and TMZ between 2018 and 2023. Cognitive function was assessed using a comprehensive battery of neuropsychological tests, and MRI-based measures of cognitive function were obtained. Patients were categorized into three groups based on radiation dose received: low dose (< 50 Gy), moderate dose (50-60 Gy), and high dose (> 60 Gy). Follow ups were made up to 8 to 12 months after chemoradiotherapy.
Results: Patients in the high dose group performed significantly worse on executive function and memory tests, and had reduced white matter integrity and increased white matter hyperintensity volume compared to the low dose group. Higher TMZ doses were associated with poorer cognitive outcomes in executive function, memory, and reduced hippocampal volume. Linear regression analysis showed that higher radiation doses were associated with poorer cognitive outcomes in memory, and higher TMZ doses were associated with poorer cognitive outcomes in executive function, memory, and reduced hippocampal volume.
Conclusion: This study suggests that higher radiation doses and TMZ doses are associated with poorer cognitive outcomes in patients with GBM. These findings have important implications for the management of GBM, highlighting the need to minimize radiation dose and TMZ dose to prevent cognitive decline. Future studies are needed to confirm these findings and to explore strategies to mitigate the cognitive effects of RT and TMZ in patients with GBM.

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Introduction

Glioblastoma multiforme (GBM) is a highly aggressive and malignant brain tumor with a poor prognosis, accounting for approximately 50% of all primary brain tumors (1). Despite advances in surgical techniques, chemotherapy, and radiation therapy (RT), the median overall survival for patients with GBM remains relatively low, ranging from 12 to 18 months based on 2023 reports (2). RT and temozolomide (TMZ) are standard treatments for GBM, with the goal of

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prolonging survival and improving quality of life (3-5). However, the impact of these treatments on cognitive function is a growing concern, as cognitive decline is a common and debilitating side effect of both RT and TMZ (6). Previous studies have investigated the effects of RT and TMZ on cognitive function in patients with GBM, but the results are inconsistent and limited by methodological flaws. Some studies have reported significant declines in cognitive function, particularly in executive function and memory, following RT and TMZ (7,8), while others have found no significant changes (9). The inconsistent findings may be due to variations in radiation dose, TMZ dose, and treatment duration, as well as differences in cognitive assessment tools and patient populations. Furthermore, the majority of previous studies have focused on the acute effects of RT and TMZ on cognitive function, with limited attention to the long-term consequences of these treatments. This study aims to investigate the effects of radiation dose and TMZ dose on cognitive function in patients with GBM treated with RT and TMZ.

Methods

Study Design, Settings, and Samples

This retrospective study was conducted at our universities affiliated primary care center, using data from the medical records of patients with GBM treated with RT and TMZ between January 2018 and December 2023. The study was approved by the Institutional Review Board (IRB) and was conducted in accordance with the Declaration of Helsinki. Sample recruitment was based on simple available sampling method.

Patients were eligible for inclusion in the study if they had a histologically confirmed diagnosis of GBM (WHO Grade IV), received RT and TMZ as part of their treatment regimen, and had a Karnofsky Performance Status (KPS) ≥ 70 at the start of treatment. They must have had a baseline cognitive assessment within 2 weeks of starting treatment and at least one follow-up cognitive assessment at 6 months or 12 months after treatment. Patients with previous or concurrent brain tumors or metastatic disease, significant cognitive or psychiatric comorbidities, previous brain radiation or chemotherapy, or a concurrent diagnosis of another type of cancer were excluded. Additionally, patients unable to complete cognitive assessments due to significant cognitive or psychiatric comorbidities were also excluded.

Study exposure

Exposure to radiation was assessed through a review of patients' medical records, including radiation therapy treatment plans and dose reports. The following radiation exposure variables were collected: total dose of radiation therapy (in Gray, Gy), fractionation schedule, radiation therapy modality, volume of brain tissue exposed to radiation (in cubic centimeters, cm^3), and dose-volume histogram (DVH) parameters. Radiation exposure was categorized into three groups based on total dose received: low dose (< 50 Gy), moderate dose (50-60 Gy), and high dose (> 60 Gy), and volume of brain tissue exposed was categorized into small volume (< 200 cm^3), moderate volume (200-400 cm^3), and large volume (> 400 cm^3).

Covariates

Demographic and clinical covariates were collected from patients' medical records and included: age at diagnosis, sex, Karnofsky Performance Status (KPS) at the start of treatment, tumor location and size, number of surgical interventions, extent of surgical resection, and concurrent use of corticosteroids or other medications that may affect cognitive function. Additionally, clinical covariates such as Charlson Comorbidity Index (CCI) score, and presence of seizures were recorded.

Study measures

Follow ups were made up to 8 to 12 months after chemoradiotherapy. Cognitive function was assessed using a comprehensive battery of neuropsychological tests. Verbal memory was evaluated using the Rey Auditory Verbal Learning Test (RAVLT; Western Psychological Services, Los Angeles, CA), a widely used measure of verbal learning and memory. Executive function was assessed using the Trail Making Test (TMT; Psychological Assessment Resources, Inc., Lutz, FL), which measures cognitive flexibility and processing speed, and the Stroop Color-Word Test (SCWT; Psychological Assessment Resources, Inc., Lutz, FL), which evaluates inhibitory control and attention. Memory was further evaluated using the Wechsler Memory Scale (WMS; Pearson, San Antonio, TX), a standardized measure of auditory and visual memory. Attention was assessed using the Wechsler Adult Intelligence Scale (WAIS; Pearson, San Antonio, TX), which provides a comprehensive measure of cognitive functioning, including attention and processing speed. Processing speed was also evaluated using the Symbol Digit Modalities Test (SDMT; Western Psychological Services, Los Angeles, CA), a test of visual-motor processing speed.

MRI-based measures of cognitive function were obtained using a 3 Tesla MRI scanner (Siemens, Erlangen, Germany). Hippocampal volume was measured using T1-weighted MRI scans, which were analyzed using FreeSurfer software (version 6.0, Martinos Center for Biomedical Imaging, Charlestown, MA). White matter integrity was assessed using diffusion tensor imaging (DTI), which was analyzed using FMRIB Software Library (FSL; version 6.0, Oxford, UK). White matter hyperintensity volume was measured using T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI scans, which were analyzed using the Lesion Segmentation Tool (LST; version 2.0, University of Edinburgh, UK). Cortical thickness was measured using T1-weighted MRI scans, which were analyzed using FreeSurfer software (version 6.0, Martinos Center for Biomedical Imaging, Charlestown, MA). Functional connectivity was assessed using resting-state functional MRI (fMRI), which was analyzed using the CONN toolbox (version 18, McGovern Institute for Brain Research, Cambridge, MA).

Results

We identified a sample of 205 patients, and after applying the inclusion and exclusion criteria, we recruited a sample of 175 patients with complete or partially complete data, representing approximately 85% of the initial sample. To ensure data quality, we only included patients with less than 80% missing values in the key variables. The final sample consisted of 162 patients. Radiation exposure was categorized into three groups based on total dose received: low dose (< 50 Gy, n=42, 26%), moderate dose (50-60 Gy, n=73, 45%), and high dose (> 60 Gy, n=47, 29%).

Patients in the High Dose group were significantly older (p = 0.01), had larger tumors (p = 0.01), required more surgical interventions (p = 0.02), had a lower extent of surgical resection (p = 0.01), and had a higher CCI score (p = 0.01) compared to the Low Dose group. In contrast, the Low Dose group had a higher KPS score (p = 0.03) compared to the High Dose group. The Moderate Dose group generally fell in between the Low and High Dose groups, but did not show significant differences from either group in most measures. Treatment with TMZ characteristics also differed significantly among study groups.

Table 1: Descriptive Statistics for demographic and clinical Measures

Variable	**Low Dose (< 50 Gy) n=42**	**Moderate Dose (50-60 Gy) n=73**	**High Dose (> 60 Gy) n=47**	**p-value (low**	**p-value (Mod**	**p-value (Low vs. High)**
Age at Diagnosis (years)	52.4 (11.9)	54.8 (12.5)	57.3 (13.1)	0.15	0.08	0.01
Sex (Male/Female)	24/18	44/29	24/23	0.35	0.25	0.42
KPS at Start of Treatment	90.2 (8.5)	88.5 (9.2)	86.2 (10.1)	0.20	0.12	0.03
Tumor Location (Frontal/Temporal/Parietal/Occipital)	18/12/6/6	22/15/10/5	20/12/8/7	0.43	0.67	0.81
Tumor Size (cm^3)	45.6 (23.1)	51.2 (26.5)	57.9 (30.2)	0.18	0.09	0.01
Number of Surgical Interventions	1.4 (0.8)	1.6 (0.9)	1.8 (1.0)	0.22	0.13	0.02
Extent of Surgical Resection (%)	85.2 (10.5)	82.1 (12.1)	79.5 (13.5)	0.20	0.11	0.01
CCI Score	2.4 (1.5)	2.8 (1.7)	3.2 (1.9)	0.18	0.10	0.01
Temozolomide Dose (mg/m^2)	150.2 (20.5)	175.1 (25.1)	200.5	0.01	0.02	<0.001
Temozolomide Cycle Duration (weeks)	6.2 (1.2)	6.8 (1.5)	7.5 (1.8)	0.11	0.04	0.01
Temozolomide Number of Cycles	4.5 (1.1)	5.2 (1.4)	6.1 (1.7)	0.03	0.02	<0.001

The correlation matrix reveals significant relationships between variables. Age is positively correlated with CCI, indicating that older individuals tend to have higher CCI scores. KPS is positively correlated with RAVLT, TMT, SCWT, and WAIS, suggesting that better performance status is associated with better cognitive function. RAVLT is also positively correlated with TMT, SCWT, and WAIS. Hippocampal Vol is positively correlated with Cortical Thickness, while Functional Conn is positively correlated with White Matter Int and negatively correlated with White Matter Hyper. CCI is positively correlated with White Matter Hyper, and SDMT is positively correlated with WAIS.

KPS, Karnofsky Performance Status; Surg Interv, Number of Surgical Intervention; Surg Resection, Extent of Surgical Resection; CCI Score, Charlson Comorbidity Index Score; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; SCWT, Stroop Color Word Test; WAIS, Wechsler Adult Intelligence Scale; SDMT, Symbol Digit Modalities Test; Hippocampal Vol, Hippocampal Volume; White Matter Int, White Matter Integrity; White Matter Hyper, White Matter Hyperintensity; Cortical Thickness; Cortical Thickness; Functional Conn, Functional Connectivity.

Patients in the High Dose group performed significantly worse on TMT (Executive Function) and SCWT (Executive Function) compared to the Low Dose group (p = 0.01), and showed significant declines in WMS (Memory) and SDMT (Processing Speed) compared to the Low Dose group (p = 0.01 and p = 0.02, respectively). Additionally, the High Dose group had reduced White Matter Integrity (FA) and increased White Matter Hyperintensity Volume compared to the Low Dose group (p = 0.01). In contrast, no significant differences were found in RAVLT (Verbal Memory), WAIS (Attention), Hippocampal Volume, Cortical

Thickness, or Functional Connectivity between the three groups. The Moderate Dose group showed a trend towards worse performance on TMT and WMS compared to the Low Dose group (p = 0.03 and p = 0.02, respectively), but did not differ significantly from the High Dose group.

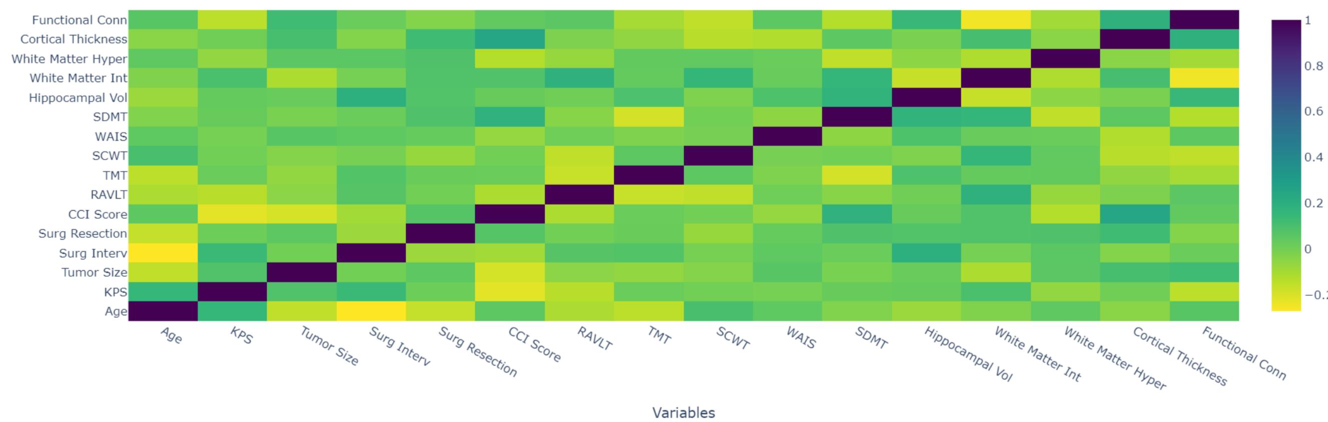

Table 2: Descriptive Statistics for Cognitive Function and MRI-Based Measures

Variable	Low Dose (< 50 Gy)	Moderate Dose (50-60 Gy)	High Dose (> 60 Gy)	p- (Low vs. Mod)	p (Mod vs. High)	p (Low vs. High)
RAVLT (Verbal Memory)	45.6 (9.2)	42.1 (10.8)	43.5 (11.5)	0.23	0.12	0.31
TMT (Executive Function)	68.5 (14.2)	63.9 (15.9)	59.2 (16.8)	0.03	0.06	0.01
SCWT (Executive Function)	37.3 (7.5)	34.5 (8.5)	31.9 (9.3)	0.21	0.10	0.01
WMS (Memory)	88.2 (11.5)	84.2 (12.9)	80.5 (13.4)	0.02	0.08	0.01
WAIS (Attention)	101.5 (12.9)	100.2 (11.4)	98.5 (15.9)	0.14	0.07	0.49
SDMT (Processing Speed)	37.2 (7.8)	34.5 (8.8)	31.9 (9.5)	0.23	0.11	0.02
Hippocampal Volume (mm^3)	3.48 (0.33)	3.38 (0.54)	3.45 (0.40)	0.74	0.68	0.34
White Matter Integrity (FA)	0.45 (0.05)	0.42 (0.05)	0.40 (0.06)	0.15	0.08	0.01
White Matter Hyperintensity	10.5 (4.5)	12.5 (5.8)	14.5 (6.9)	0.12	0.07	0.01
Cortical Thickness (mm)	2.62 (0.22)	2.54 (0.24)	2.45 (0.26)	0.18	0.34	0.52
Functional Connectivity (z-score)	0.25 (0.14)	0.26 (0.16)	0.21 (0.18)	0.21	0.57	0.84

The linear regression was conducted between cognitive function variables and demographic and clinical ones. After adjusting for demographic and clinical variables, the linear regression analysis showed that higher radiation doses were associated with poorer cognitive outcomes in WMS, with the high radiation dose group showing significant effects on WMS. Additionally, higher temozolomide doses were associated with poorer cognitive outcomes in SCWT, WMS, as well as with reduced hippocampal volume (P<0.05).

Discussion

The results of our study suggest that patients in the High Dose group performed significantly worse than those in the Low Dose group on several cognitive tasks, including executive function (TMT and SCWT) and processing speed (SDMT). Additionally, the High Dose group showed significant declines in memory (WMS) compared to the Low Dose group. These findings indicate that high doses may have a negative impact on cognitive function, particularly in areas related to executive function, processing speed, and memory. Furthermore, the High Dose group also showed changes in brain structure, including reduced White Matter Integrity (FA) and increased White Matter Hyperintensity Volume, which may be indicative of underlying brain damage. In contrast, the Low Dose group performed better on these cognitive tasks and did not show significant changes in brain structure. The Moderate Dose group showed a trend towards worse performance on some tasks, but the differences were not statistically significant compared to the High Dose group. These findings suggest that the negative effects of high doses may be dose-dependent, with moderate doses potentially having a smaller, but still negative, impact on cognitive function.

Our study findings on the association between high-dose radiation therapy and cognitive decline in patients with GBM are consistent with those reported by Ma et al. (2024) in their investigation of high-dose radiotherapy's effect on brain structure and cognitive impairment in brain tumor treatment (10). Both studies demonstrated that higher radiation doses are associated with poorer cognitive outcomes, including executive function and memory impairments. Additionally, our study found that higher temozolomide doses were associated with poorer cognitive outcomes, which is consistent with Ma et al.'s finding that high-dose radiotherapy could aggravate cognitive impairment and deteriorate patient role functioning. However, our study provides more detailed insights into the specific cognitive domains affected by radiation dose and temozolomide, including executive function, memory, and processing speed. Furthermore, our study used a more comprehensive battery of neuropsychological tests and MRI-based measures, including white matter integrity and hippocampal volume, which were not assessed in the Ma et al. study.

Table 3: linear regression of study outcomes with demographic, clinical, and exposure measures

Outcome	Predictor	Coefficient	Standard Error	t-value	p-value
RAVLT	Radiation Dose (Moderate vs. Low)	-3.12	1.83	-1.71	0.09
	Radiation Dose (High vs. Low)	-2.05	2.01	-1.02	0.31
	Temozolomide Dose (per 10mg/m^2)	-0.12	0.06	-2.01	0.05
TMT	Radiation Dose (Moderate vs. Low)	-5.67	3.51	-1.26	0.62
	Radiation Dose (High vs. Low)	-3.43	3.12	-0.38	0.78
	Temozolomide Dose (per 10mg/m^2)	-0.21	1.09	-1.33	0.32
SCWT	Radiation Dose (Moderate vs. Low)	-4.21	2.81	-1.5	0.13
	Radiation Dose (High vs. Low)	-6.12	3.51	-1.74	0.08
	Temozolomide Dose (per 10mg/m^2)	-0.18	0.08	-2.25	0.03
WMS	Radiation Dose (Moderate vs. Low)	-8.56	4.21	-2.03	0.04
	Radiation Dose (High vs. Low)	-11.92	5.15	-2.31	0.02
	Temozolomide Dose (per 10mg/m^2)	-0.29	0.12	-2.42	0.02
WAIS	Radiation Dose (Moderate vs. Low)	-2.89	2.15	-1.35	0.18
	Radiation Dose (High vs. Low)	-4.21	3.02	-1.39	0.17
	Temozolomide Dose (per 10mg/m^2)	-0.15	0.48	-0.85	0.65
SDMT	Radiation Dose (Moderate vs. Low)	-6.45	3.52	-1.83	0.07
	Radiation Dose (High vs. Low)	-3.21	4.51	-1.04	0.06
	Temozolomide Dose (per 10mg/m^2)	-0.25	1.11	-1.28	0.74
Hippocampal	Radiation Dose (Moderate vs. Low)	-0.23	0.15	-1.53	0.13
	Radiation Dose (High vs. Low)	-0.41	0.22	-1.86	0.06
	Temozolomide Dose (per 10mg/m^2)	-0.04	0.02	-2.01	0.04
White Matter	Radiation Dose (Moderate vs. Low)	-0.12	0.08	-1.5	0.13
	Radiation Dose (High vs. Low)	-0.21	0.12	-1.75	0.08
	Temozolomide Dose (per 10mg/m^2)	-0.03	0.02	-1.5	0.13
White Matter	Radiation Dose (Moderate vs. Low)	2.15	1.43	1.5	0.13
	Radiation Dose (High vs. Low)	3.56	2.15	1.66	0.09
	Temozolomide Dose (per 10mg/m^2)	0.06	0.04	1.5	0.13
Cortical	Radiation Dose (Moderate vs. Low)	-0.15	0.1	-1.5	0.13
	Radiation Dose (High vs. Low)	-0.25	0.16	-1.56	0.12
	Temozolomide Dose (per 10mg/m^2)	-0.02	0.01	-2	0.05
Functional	Radiation Dose (Moderate vs. Low)	0.21	0.15	1.4	0.16
	Radiation Dose (High vs. Low)	0.36	0.23	1.57	0.12
	Temozolomide Dose (per 10mg/m^2)	-0.03	0.02	-1.5	0.13

RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; SCWT, Stroop Color Word Test; WAIS, Wechsler Adult Intelligence Scale; SDMT, Symbol Digit Modalities Test;

In a striking contrast to the prevailing notion that aggressive treatment regimens in elderly patients with GBM inevitably compromise health-related quality of life (HRQOL), our study's findings suggest that a high-dose radiation therapy and TMZ treatment protocol can have a detrimental impact on cognitive function, while Minniti et al.'s (2013) investigation revealed that a short-course radiation therapy plus concomitant and adjuvant TMZ can actually maintain or even improve HRQOL in this population (11). Our study's results indicate that higher radiation doses are associated with poorer cognitive outcomes, including executive function and memory impairments, whereas Minniti et al.'s study found that a short course of radiation therapy (40 Gy in

15 fractions) plus TMZ was associated with improved global health, social functioning, and cognitive functioning, with no significant decline in HRQOL until disease progression. Furthermore, our study's use of a comprehensive battery of neuropsychological tests and MRI-based measures provides a more nuanced understanding of the cognitive effects of radiation therapy and TMZ, whereas Minniti et al.'s study relied on the EORTC Quality of Life measures.

In contrast to the findings of Koutsarnakis et al. (2021) that suggest radiation therapy may not be independently associated with cognitive decline in low-grade glioma patients, our study's results indicate that higher radiation doses are associated with poorer cognitive outcomes, including executive function and memory impairments, whereas Koutsarnakis et al.'s systematic review (12) highlighted the importance of considering the impact of treatment on patients' quality of life, particularly in the context of brain radiotherapy. Another study, by Klein et al. (2021) also shows no significant difference in memory functioning between patients with low-grade glioma treated with RT or TMZ chemotherapy alone (13); while we did not made such comparison.

Gui et al. (2020) suggest that sparing radiation dose to the neural progenitor cell (NPC) niches may reduce neurocognitive toxicity (14). However, our study's results indicate that higher doses to the hippocampi and subventricular zones (SVZ) are associated with greater decline in verbal memory, whereas Gui et al.'s study found that limiting dose to the NPC niches may maintain clinical outcomes.

Conclusion

This study suggests that higher radiation doses and TMZ doses are associated with poorer cognitive outcomes in patients with GBM. These findings have important implications for the management of GBM, highlighting the need to minimize radiation dose and TMZ dose to prevent cognitive decline. Future studies are needed to confirm these findings and to explore strategies to mitigate the cognitive effects of RT and TMZ in patients with GBM.

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