Advances in Radiation Oncology (2025) **10**, 101717

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Reduced Treatment Volumes for Glioblastoma Associated With Lower Rates of Radionecrosis and Lymphopenia: A Pooled Analysis

Jennifer K. Matsui, MD, PhD,[a] David Swanson, PhD,[b] Pamela Allen, PhD,[b] Haley K. Perlow, MD,[c] Jared Bradshaw, BS,[c] Thomas H. Beckham, MD, PhD,[b] Martin C. Tom, MD,[b] Chenyang Wang, MD, PhD,[b] Subha Perni, MD,[b] Debra N. Yeboa, MD,[b] Amol J. Ghia, MD,[b] Mary Frances McAleer, MD, PhD,[b] Jing Li, MD, PhD,[b] Joshua D. Palmer, MD,[c] and Susan L. McGovern, MD, PhD[b,*]

[a]*Department of Radiation Oncology, Stanford University, Stanford, California;* [b]*Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; and* [c]*Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, Ohio*

Received 23 August 2024; accepted 3 January 2025

Purpose: There is marked variability in treatment fields for glioblastoma. We performed a retrospective study comparing outcomes of patients treated according to MD Anderson Cancer Center (MDACC) or Radiation Therapy Oncology Group (RTOG) guidelines and identified differences in treatment-related toxicity.

Methods and Materials: Adult patients with glioblastoma treated with surgery and adjuvant radiation treatment were included in this study. Primary outcomes were local control, progression-free survival (PFS), overall survival (OS), and radiation-related toxicity. PFS and OS were estimated using the Kaplan-Meier estimator. Univariate and multivariate analyses were conducted using Cox regression models.

Results: In total, 257 patients met the inclusion criteria with a median age of 60.1 years at diagnosis. There were 162 and 95 patients treated according to the MDACC or RTOG guidelines, respectively. Despite having similar gross tumor volumes, the RTOG cohort had a larger median planning target volume (303.2 cm^3 vs 430.7 cm^3, $P < .001$) and worse PFS (6 months vs 9 months, $P = .031$). There was no difference in OS between treatment techniques. Patients treated according to RTOG guidelines experienced higher rates of radionecrosis (34% vs 21%, $P = .024$) and severe lymphopenia (15% vs 7%, $P = .044$).

Conclusions: Patients treated according to MDACC guidelines had smaller treatment volumes, improved PFS, and lower rates of radionecrosis and severe lymphopenia. However, when adjusting for prognostic factors, treatment type was not associated with PFS in multivariate analysis. Prospective investigation is warranted to confirm these differences in outcomes.

Sources of support: This research was supported in part by The University of Texas MD Anderson Cancer Center, P30CA016672, and the RSNA Medical Student Grant (JKM).

Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Susan L. McGovern, MD, PhD; Email: slmcgove@mdanderson.org

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults, constituting 14.5% of all central nervous system tumors and nearly half of

https://doi.org/10.1016/j.adro.2025.101717

malignant central nervous system tumors.[1,2] GBM carries a heavy treatment burden and poor prognosis, with a median overall survival (OS) of 15 months.[3] The current standard of care for newly diagnosed GBM in adults is maximal safe resection followed by radiation therapy (RT) with concurrent and adjuvant temozolomide.[4]

According to the American Society of Clinical Oncology guidelines, there are 2 acceptable strategies for RT of GBM in 30 fractions.[5] The first, used in Radiation Therapy Oncology Group (RTOG) trials, employs a sequential cone-down approach. The initial treatment volume includes gross residual disease, surgical cavity, and peritumoral edema with a 2 cm clinical target volume (CTV) margin, treated to an initial dose of 46 Gy. This is followed by a cone-down boost to a total dose of 60 Gy to gross residual disease and the cavity.[6] The second approach, used at MD Anderson Cancer Center (MDACC), is a simultaneous integrated boost technique with 2 dose levels: 60 Gy to the gross residual disease and cavity and 50 Gy to the CTV, defined as an anatomically constrained 2 cm expansion on the cavity and residual enhancing disease, without explicit coverage of peritumoral edema.[7]

Currently, there is marked variability between institutions when defining CTVs, and there is ongoing debate regarding the advantages and risks of tightened treatment volumes. Wernicke et al[8] asked the question, "How small is large enough?" The authors reviewed patterns of recurrence and outcomes of patients treated with larger volumes versus limited margins and found that limited margins did not result in inferior survival or recurrence patterns. A study by Chang et al[6] compared patients who were treated according to RTOG and MDACC 60 Gy target volumes and found recurrences were covered in 99% and 95% of the cases, respectively ($P = .1$). Furthermore, the authors found that the proportion of edema that overlapped with recurrent tumor was 23%, leading to the conclusion that the inclusion of peritumoral edema in the CTV led to excessive irradiation of normal brain tissue.

In addition to outcome differences, we were also interested in exploring the differences in radiation-related toxicities between the MDACC and RTOG approaches. Numerous studies have found that lymphopenia is associated with poor prognosis in a variety of cancers, including glioma.[9-12] Furthermore, retrospective studies have demonstrated that the volume of radiated tissue is associated with high-grade radiation-induced lymphopenia.[13-15]

In this study, we pooled patients treated at 2 institutions to compare treatment technique outcomes and rates of radiation-related toxicity. We hypothesized that patients who were treated according to the MDACC protocol would have smaller treatment volumes but no significant differences in recurrence or OS. Finally, we sought to identify if there were significant differences in rates of radiation-related toxicities between the MDACC and RTOG protocols.

Methods and Materials

Patient selection

This study was approved by the institutional review boards at both MDACC and the Ohio State University Wexner Medical Center. We included adult patients (≥18 years) with biopsy-proven GBM and a Karnofsky performance status (KPS) score of ≥70 who were treated with RT at each institution. Patients with an R132H IDH1 mutation, hypofractionated treatment regimen, total dose < 59.4 Gy, prior RT, and a KPS score < 70 were excluded. Demographic, clinical, toxicity, and outcome data were collected for each patient.

RT protocols

Patients were treated with intensity modulated RT or volumetric modulated arc therapy with treatment volumes defined according to either the MDACC or RTOG protocol. The selection of the treatment technique was based on institutional preference, which varied by provider and institution.

In the MDACC technique, the gross tumor volume (GTV) includes the cavity and residual enhancement. The CTV is a 2 cm anatomically constrained expansion on the GTV that does not include peritumoral edema. The planning target volume (PTV)_boost is a 3 mm geometric expansion on the GTV, and the PTV is a 3 mm geometric expansion on the CTV. Using a simultaneous integrated boost approach, the PTV_boost is treated to 60 Gy, and the PTV is treated to 50 Gy; both volumes are treated in 30 fractions.

The RTOG approach uses a sequential cone-down technique where the initial CTV includes a 2 cm anatomically constrained expansion on the GTV, which includes the cavity, residual enhancement, and peritumoral edema. A 3 to 5 mm geometric margin is added to the CTV to generate the PTV. This PTV is treated to 46 Gy in 23 fractions. The boost volume, encompassing only the cavity and residual enhancement, is then treated with an additional 14 Gy in 7 fractions with a margin. Figures comparing the MDACC and RTOG treatment volumes are in a report by Chang et al.[6]

Treatment-related toxicity

Radionecrosis was characterized through either surgical pathology or magnetic resonance imaging using available perfusion and diffusion techniques. Lymphopenia was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 as grade 0 (greater than or equal to the lower limit of normal), grade 1 (lower than the lower limit of normal to $\geq 0.8 \times 10^9$ cells/

L), grade 2 (<0.8 to ≥0.5 × 10^9 cells/L), grade 3 (<0.5 to ≥0.2 × 10^9 cells/L), and grade 4 (<0.2 × 10^9 cells/L), all nadir values. The time frame for assessing grade 3 lymphopenia was defined as from the start of RT to 1 month after the completion of RT. Other radiation-related toxicities (eg, fatigue and dermatitis) were quantified by the provider during follow-up appointments using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 and graded on a scale from 0 to 5.

Statistical methods

Statistical analysis was performed using R and RStudio.[16] Patient characteristics including gender, median age at diagnosis, KPS prior to RT, MGMT (O^6-methylguanine-DNA-methyltransferase) status, GTV, initial phase PTV, use of concurrent chemotherapy, hospitalization following RT, steroid use during RT, steroid use after RT, recurrence after RT, recurrence type, radionecrosis, and lymphopenia were compared. Local recurrence was defined at or near the site of the treated tumor in the high-dose radiation field. OS was calculated from the end of RT to the date of death or last follow-up. Progression-free survival (PFS) was calculated from the end of RT to the documentation of progression or last follow-up for patients who did not experience progression. PFS was defined as the time until the development of a new lesion or ≥25% increase in previously identified enhancing lesions.[17] Pearson's χ^2 test was used to compare variables between the MDACC and RTOG protocol groups in the frequency table. The Kaplan-Meier method was used to estimate PFS and OS. PFS was defined as the time from the end of RT to progression based on magnetic resonance imaging or tissue confirmation. Age, MGMT status, performance status at the time of treatment, extent of resection, radiation technique, concurrent chemotherapy (yes vs no), and severe lymphopenia were included in the univariate analyses. Variables that were significant in univariate analysis at the .05 level were included in the multivariate analysis. The Cox proportional hazard model was used to conduct univariate and multivariate analyses.

Results

Patient characteristics and outcomes

A total of 257 patients diagnosed with GBM from 2013 to 2016, including those treated with RT at either institution, were eligible for analysis. Patient characteristics and outcomes are described in Table 1.

The MDACC and RTOG cohorts had similar distributions of patient age, gender, KPS, and MGMT methylation status. The GTV volume was also similar between the groups, but the RTOG group had a significantly larger median PTV (430.7 cm^3 vs 303.2 cm^3, $P < .001$). Despite this, the rate of recurrence was higher in the RTOG cohort than in the MDACC cohort (86% vs 71%, $P = .006$). There was no difference in the rate of local versus distant recurrences between cohorts.

The overall median PFS and OS were 7 and 15 months, respectively (Fig. 1A, B). The overall median OS at 12 and 24 months were 60% and 29%, respectively. The median PFS and OS for the MDACC cohort were 9 and 16 months, respectively. The median PFS and OS for the Ohio State University Wexner Center cohort were 6 and 14 months, respectively. The use of the log-rank test suggested that patients treated according to the MDACC protocol had improved PFS ($P = .031$), but no significant difference was found in OS ($P = .11$) (Fig. 1C, D).

Univariate and multivariate analysis

In univariate analysis, older age and treatment according to the RTOG protocol predicted worse PFS (Table 2). MGMT methylation, KPS ≥ 80, and gross total resection were associated with improved PFS. Multivariate analyses suggested age and methylation status persisted as significant variables (Table 3); older age was associated with poorer PFS (hazard ratio [HR], 1.02 for a 1-year increase in age; $P = .019$; 95% CI, 1.00-1.04), and MGMT methylation was associated with better PFS (HR, 0.35; $P \leq .001$; 95% CI, 0.25-0.49); all HRs were conditional on the covariates in the model.

Factors associated with improved OS in univariate analysis were age as a continuous variable, MGMT status, KPS, and extent of resection (Table 4). Multivariate analysis suggested that older age was associated with worse OS (HR, 1.03; $P \leq .001$; 95% CI, 1.02-1.05) and MGMT methylation (HR, 0.40; $P \leq .001$; 95% CI, 0.29-0.56), and KPS ≥ 80 (HR, 0.65; $P = .007$; 95% CI, 0.47-0.89) was associated with superior OS (Table 5).

Treatment-related toxicity

Table 1 demonstrates that the rates of radionecrosis (34% vs 21%, $P = .024$) and grade 3+ lymphopenia (15% vs 7%, $P = .044$) were higher in the RTOG group. Three patients experienced other grade 3 radiation-related toxicities. One patient from the RTOG cohort had grade 3 thrombocytopenia, and another patient treated according to MDACC guidelines had grade 3 fatigue. The most common grade 1 to 2 radiation-related toxicities were fatigue (n = 174), dermatitis (n = 92), headaches (n = 83), and nausea (n = 54).

Discussion

In this retrospective analysis, we compared clinical outcomes and treatment-related toxicities in patients with

Table 1 Patient characteristics and outcomes

Attribute	Total (%)	One-phase (%)	Two-phase (%)	*P* value
n	257	162	95	
Gender				.089
Male	153 (60)	103 (64)	50 (53)	-
Female	104 (40)	59 (36)	45 (47)	-
Median age at diagnosis (IQR), y	60.1 (52.5-64.6)	59.8 (51.8-65.6)	60.1 (54.2-62.9)	.487
KPS prior to RT				.550
100	42 (16)	21 (13)	21 (22)	-
90	123 (48)	90 (56)	33 (35)	-
80	64 (25)	36 (22)	28 (29)	-
70	28 (11)	15 (9)	13 (14)	-
MGMT				.890
Unmethylated	130 (60)	78 (61)	52 (60)	-
Methylated	85 (40)	50 (39)	35 (40)	-
GTV (IQR)	35.3 (20.7-57.0)	35.3 (20.0-54.3)	38.1 (22.4-60.2)	.312
PTV, initial phase (IQR)	342.8 (256.0-453.3)	303.2 (238.0-409.6)	430.7 (290.7-563.3)	<.001
Concurrent chemotherapy				.304
No	3 (1)	3 (2)	0 (0)	-
Yes	254 (99)	159 (98)	95 (100)	-
Hospitalization following RT				.185
No	120 (47)	81 (50)	56 (59)	-
Yes	137 (53)	81 (50)	31 (33)	-
Steroids during RT				.783
No	80 (31)	49 (30)	31 (33)	-
Yes	177 (69)	113 (70)	64 (67)	-
Steroids after RT				.533
No	144 (56)	88 (54)	56 (59)	-
Yes	113 (44)	74 (46)	39 (41)	-
Recurrence after RT				.006
No	60 (23)	47 (29)	13 (14)	-
Yes	199 (77)	117 (71)	82 (86)	-
Recurrence type				.562
Local	154 (78)	93 (79)	62 (76)	-
Distant	44 (22)	24 (21)	20 (24)	-
Radionecrosis				.024
No	191 (74)	128 (79)	63 (66)	-
Yes	66 (26)	34 (21)	32 (34)	-
Lymphopenia (grade 3+)				.044
No	190 (90)	124 (93)	66 (85)	-
Yes	21 (10)	9 (7)	12 (15)	-

Abbreviation: GTV = gross tumor volume, KPS = Karnofsky Performance Status, MGMT = O^6-methylguanine-DNA-methyltransferase, PTV = planning target volume, RT = radiation therapy.

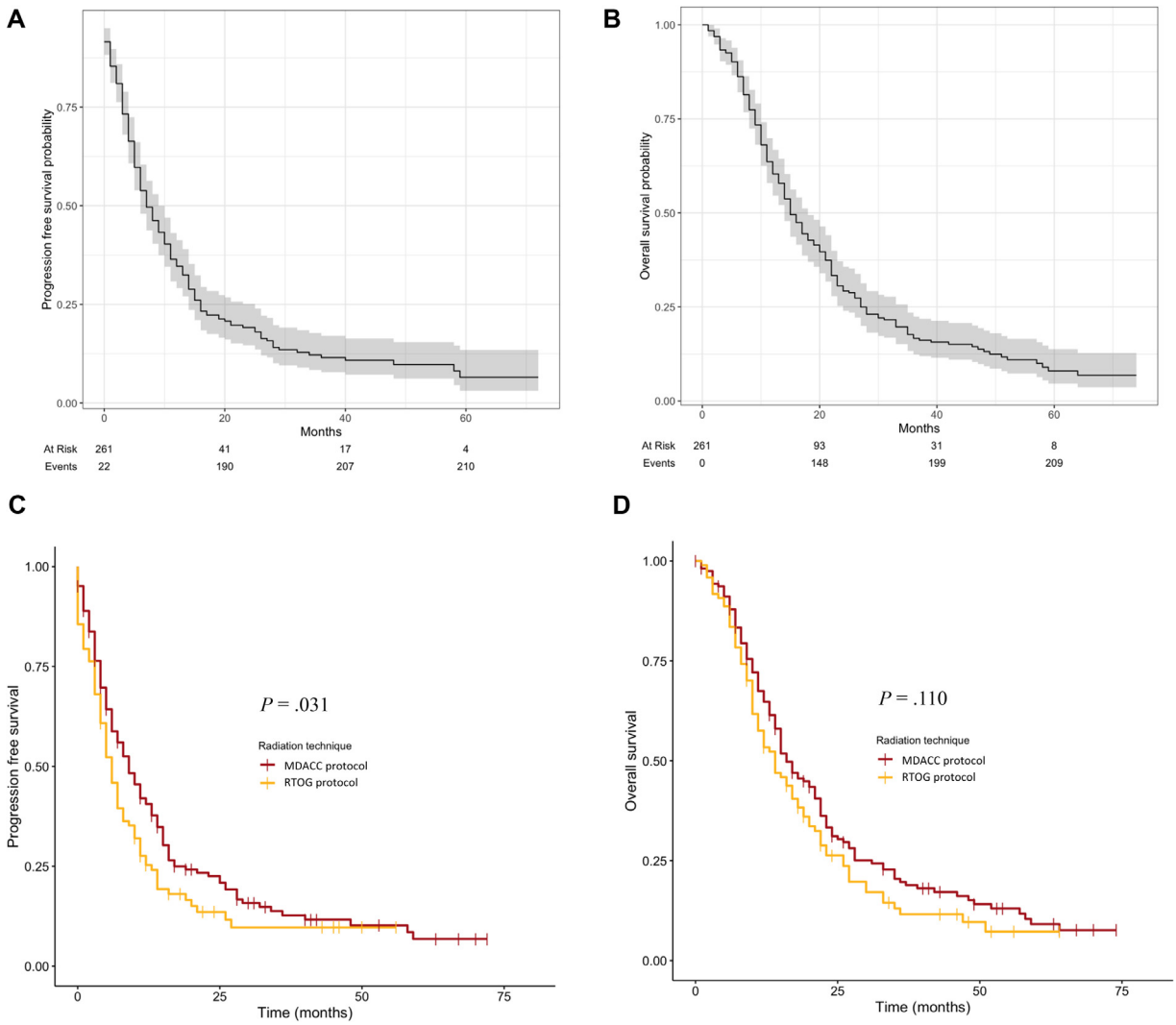

Figure 1 Kaplan-Meier curves for (A) progression-free survival and (B) overall survival for all cases and (C) progression-free survival and (D) overall survival stratified by radiation technique.

GBM treated according to MDACC or RTOG guidelines. Consistent with our hypothesis, the MDACC group had smaller treatment volumes and lower rates of radionecrosis and severe lymphopenia than the RTOG group.

There is considerable variability in target delineation for GBM. To our knowledge, this is the largest study comparing survival outcomes and radiation-related toxicities between patients treated according to the MDACC and RTOG guidelines. Although patients treated according to RTOG protocol had significantly larger PTVs, there was no associated survival benefit. Notably, the RTOG cohort experienced worse PFS with higher rates of radionecrosis and grade 3+ lymphopenia. In contrast, the MDACC protocol reduced radiation exposure to the brain, thereby minimizing radiation-related toxicities. Given the poor prognosis of GBM, maintaining survival while preserving quality of life is a desired outcome.

In our study, the median GTVs between the MDACC and RTOG cohorts were similar (35.3 cm^3 vs 38.1 cm^3), but the median PTV was significantly larger in the RTOG group. Our findings are in accordance with a report by Chang et al,[6] where the median volume of brain irradiated to 60 Gy was significantly higher in the RTOG group versus MDACC (16% vs 7%, $P = .001$). A separate small prospective study compared the 2 techniques and also found a significantly higher average V60 in the RTOG arm (356.8 cm^3 vs 255.5 cm^3).[18]

We also found that patients treated according to MDACC guidelines had lower rates of disease recurrence (71% vs 86%, $P = .006$); patterns of failure (eg, local or distant) were similar between the 2 groups. A study by Minniti et al[19] analyzed recurrence patterns in 207 patients who were treated according to European SocieTy for Radiotherapy and Oncology target volume delineation guidelines

Table 2 Progression-free survival: univariate analysis

Progression-free survival				
Covariables	**Comparison group**	**HR**	**95% CI**	***P* value**
Age (continuous variable)	-	1.02	1.00-1.03	.039
MGMT status				
Methylated	Unmethylated	0.38	0.27-0.52	<.001
Performance status				
≥80	<80	0.74	0.56-0.98	.037
Extent of resection				
Gross total	Subtotal	0.65	0.490.86	.003
Radiation technique				
Two-phase	One-phase	1.36	1.03-1.80	.030
Concurrent chemotherapy				
Yes	No	0.80	0.20-3.25	.760
Severe lymphopenia				
Yes	No	1.47	0.90-2.40	.125

Abbreviation: HR = hazard ratio, MGMT = O^6-methylguanine-DNA-methyltransferase.

Table 3 Progression-free survival: multivariate analysis

Progression-free survival				
Covariables	**Comparison group**	**HR**	**95% CI**	***P* value**
Age (continuous variable)	-	1.02	1.00-1.04	.019
MGMT status				
Methylated	Unmethylated	0.35	0.25-0.49	<.001

Abbreviation: HR = hazard ratio, MGMT = O^6-methylguanine-DNA-methyltransferase.

Table 4 Overall survival: univariate analysis

Overall survival				
Covariables	**Comparison group**	**HR**	**95% CI**	***P* value**
Age (continuous variable)	-	1.03	1.02-1.05	<.001
MGMT status				
Methylated	Unmethylated	0.49	0.35-0.67	<.001
Performance status				
≥80	<80	0.59	0.45-0.78	<.001
Extent of resection				
Gross total	Subtotal	0.65	0.49-0.87	.004
Radiation technique				
Two-phase	One-phase	1.25	0.95-1.65	.115
Concurrent chemotherapy				
Yes	No	0.94	0.23-3.81	.936
Severe lymphopenia				
Yes	No	1.60	0.98-2.62	.061

Abbreviation: HR = hazard ratio, MGMT = O^6-methylguanine-DNA-methyltransferase.

Table 5 Overall survival: multivariate analysis

Overall survival				
Covariables	**Comparison group**	**HR**	**95% CI**	***P* value**
Age (continuous variable)	-	1.03	1.02-1.05	<.001
MGMT status				
Methylated	Unmethylated	0.40	0.29-0.56	<.001
Performance status				
≥80	<80	0.65	0.47-0.89	.007

Abbreviation: HR = hazard ratio, MGMT = O^6-methylguanine-DNA-methyltransferase.

with a 2 cm margin around the GTV. After plans were revised to a 1 cm margin, the dosimetric analysis revealed similar patterns of failure with a significantly lower median CTV (136.5 cm^3 vs 234.6 cm^3, $P \leq .0001$).

Given the significant differences in treatment volumes, we hypothesized there may be variations in radiation-related toxicities between the protocol groups. Rates of radionecrosis were higher in the RTOG group (34% vs 21%, $P = .024$). Although radionecrosis can be managed with steroids, some instances may require surgical resection.[20] Rates of grade 3+ lymphopenia were also higher in the RTOG cohort (15% vs 7%). In our study, severe lymphopenia trended toward decreased OS ($P = .061$) in univariate analysis. A separate study of patients with high-grade gliomas treated with definitive RT and concurrent temozolomide found acute lymphopenia (grade 3 to 4) was associated with significantly worse OS (median, 12.5 vs 20.2 months, $P \leq .001$).[14] The authors also reported a strong association between lymphopenia development and higher brain volumes receiving 25 Gy.

Although our study did not capture dose to critical structures or neurocognitive changes following RT, prior studies indicate that smaller CTVs can significantly decrease the dose to the hippocampus, which would be expected to reduce the neurocognitive and quality-of-life impact of radiation.[19,21-23] Minniti et al's[19] study demonstrated a notable difference in median hippocampal dose between the original 2 cm margin and a theoretical 1 cm margin (33.7 vs 22.3 Gy, $P < .0001$). In a prospective study by Kumar et al,[18] patients treated according to MDACC guidelines exhibited significantly better quality of life, as assessed by the European Organisation For Research And Treatment Of Cancer Quality of Life Questionnaire.

Within our cohort, patients treated per MDACC guidelines demonstrated superior PFS by the log-rank test ($P = .031$). Although the radiation technique was not independently prognostic for PFS in multivariate analysis, this finding aligns with the report by Kumar et al,[18] indicating improved median PFS with the MDACC approach compared with RTOG (8.8 vs 6.1 months, $P = .043$).

Recent discussions emphasize the need to standardize the definition of CTVs and minimize irradiation of normal brain tissue, especially if survival outcomes are comparable.[24] Trifiletti et al[24] highlighted 2 potential strategies: using smaller CTV margins or employing novel imaging techniques to selectively irradiate specific parts of the brain,[25] aiming to reduce radiation-related toxicity. In response to Trifiletti et al's[24] article, Kotecha and Mehta[26] highlighted the variability in target volume delineation and cautioned that smaller CTV expansions might not adequately cover tracts of direct tumor spread, such as the anterior corpus callosum. They also noted the potential movement of the tumor and cavity during treatment, which could exceed 5 mm. These considerations underscore the importance of a nuanced approach when evaluating and implementing changes in treatment strategies to achieve optimal outcomes.

There are several limitations to our study. The retrospective nature introduces potential selection biases, and our sample size may limit the generalizability of our findings. Furthermore, data on toxicity grading were retrospectively assigned, and radionecrosis included patients who were both asymptomatic and symptomatic. Furthermore, radionecrosis may be a mixture of viable tumor and treatment effects, and not all patients underwent biopsy for pathologic confirmation. We were not able to account for potential differences in treatment eras, providers, institutions, or patient- and tumor-related characteristics that could influence the choice of treatment technique. Additionally, the inclusion of patients treated from 2013 to 2016 might not reflect the most current practices or emerging treatment modalities. Although we only included patients with biopsy-proven GBM who did not have the R132H IDH1 mutation, there is a chance of a noncanonical IDH mutant tumor. Noncanonical IDH mutant tumors are typically found in younger patient populations, making this scenario less likely in our patient population.[27] Given the retrospective nature of the study, we were unable to collect data regarding patients' cognition or quality of life following RT. We were also unable to collect detailed dosimetric volumes, such as brain V25. Local and distant progression was documented based on imaging, biopsy, and/or chart documentation, but we did not distinguish in-field, marginal, and out-of-field treatment failure.

Conclusions

In conclusion, our study found that patients treated according to MDACC guidelines had smaller treatment volumes and lower rates of radiation-induced toxicity, including radionecrosis and severe lymphopenia, with similar PFS and OS compared with RTOG volumes. These findings suggest that smaller treatment volumes employed in the MDACC approach may mitigate treatment-related toxicity without negatively impacting survival outcomes. As we navigate the delicate balance between reducing treatment volumes and minimizing disease spread risk, these findings underscore the need for more refined target delineation in GBM.

Disclosures

Dr. McGovern has a relationship with Chimerix. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of AI and AI-Assisted Technologies in the Writing Process

AI and/or AI-Assisted Technologies were not used in the writing process.

References

1. Grochans S, Cybulska AM, Simińska D, et al. Epidemiology of glioblastoma multiforme—Literature review. *Cancers (Basel)*. 2022;14:2412.
2. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009—2013. *Neuro Oncol*. 2016;18:v1-v75.
3. Koshy M, Villano JL, Dolecek TA, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries. *J Neurooncol*. 2012;107:207-212.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
5. Sulman EP, Ismaila N, Chang SM. Radiation therapy for glioblastoma: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology Guideline. *J Oncol Pract*. 2017;13:123-127.
6. Chang EL, Akyurek S, Avalos T, et al. Evaluation of peritumoral edema in the delineation of radiotherapy clinical target volumes for glioblastoma. *Int J Radiat Oncol Biol Phys*. 2007;68:144-150.
7. Niyazi M, Brada M, Chalmers AJ, et al. ESTRO-ACROP guideline "target delineation of glioblastomas. *Radiother Oncol*. 2016;118:35-42.
8. Wernicke AG, Smith AW, Taube S, Mehta MP. Glioblastoma: Radiation treatment margins, how small is large enough? *Pract Radiat Oncol*. 2016;6:298-305.
9. Cho O, Oh YT, Chun M, Noh OK, Hoe JS, Kim H. Minimum absolute lymphocyte count during radiotherapy as a new prognostic factor for nasopharyngeal cancer. *Head Neck*. 2016;38(suppl 1):E1061-E1067.
10. Tang C, Liao Z, Gomez D, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys*. 2014;89:1084-1091.
11. Wu ES, Oduyebo T, Cobb LP, et al. Lymphopenia and its association with survival in patients with locally advanced cervical cancer. *Gynecol Oncol*. 2016;140:76-82.
12. Davuluri R, Jiang W, Fang P, et al. Lymphocyte nadir and esophageal cancer survival outcomes after chemoradiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;99:128-135.
13. Wang X, van Rossum PSN, Chu Y, et al. Severe lymphopenia during chemoradiation therapy for esophageal cancer: Comprehensive analysis of randomized phase 2B trial of proton beam therapy versus intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2024;118:368-377.
14. Huang J, DeWees TA, Badiyan SN, et al. Clinical and dosimetric predictors of acute severe lymphopenia during radiation therapy and concurrent temozolomide for high-grade glioma. *Int J Radiat Oncol Biol Phys*. 2015;92:1000-1007.
15. Upadhyay R, Venkatesulu BP, Giridhar P, et al. Risk and impact of radiation related lymphopenia in lung cancer: A systematic review and meta-analysis. *Radiother Oncol*. 2021;157:225-233.
16. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2023.
17. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in Neuro-Oncology Working Group. *J Clin Oncol*. 2010;28:1963-1972.
18. Kumar N, Kumar R, Sharma SC, et al. Impact of volume of irradiation on survival and quality of life in glioblastoma: A prospective, phase 2, randomized comparison of RTOG and MDACC protocols. *Neurooncol Pract*. 2020;7:86-93.
19. Minniti G, Tini P, Giraffa M, et al. Feasibility of clinical target volume reduction for glioblastoma treated with standard chemoradiation based on patterns of failure analysis. *Radiother Oncol*. 2023;181:109435.
20. Yang X, Ren H, Fu J. Treatment of radiation-induced brain necrosis. *Oxid Med Cell Longev*. 2021;2021:4793517.
21. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. *Nat Med*. 2002;8:955-962.
22. Mizumatsu S, Monje ML, Morhardt DR, Rola R, Palmer TD, Fike JR. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res*. 2003;63:4021-4027.
23. Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res*. 2004;162:39-47.
24. Trifiletti DM, Milano MT, Redmond KJ, Pollom EL, Hattangadi-Gluth JA, Kim MM. Treatment planning expansions in glioblastoma: How less can be more. *Int J Radiat Oncol Biol Phys*. 2023;117:293-296.
25. Laack NN, Pafundi D, Anderson SK, et al. Initial results of a phase 2 trial of 18F-DOPA PET-guided dose-escalated radiation therapy for glioblastoma. *Int J Radiat Oncol Biol Phys*. 2021;110:1383-1395.
26. Kotecha R, Mehta MP. In regard to Trifiletti et al. *Int J Radiat Oncol Biol Phys*. 2024;118:575-577.
27. Poetsch L, Bronnimann C, Loiseau H, et al. Characteristics of IDH-mutant gliomas with non-canonical IDH mutation. *J Neurooncol*. 2021;151:279-286.