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A Comparative Study between Delineation of Radiotherapy Target Volumes with and Without Peritumoral Edema for Patients with Postoperative Glioblastoma Multiforme

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Abstract

Background: Glioblastoma Multiforme (GBM) is an aggressive primary brain tumor with a poor prognosis. Radiotherapy is a critical component of GBM treatment, but the optimal delineation of the clinical target volume (CTV), particularly regarding the inclusion of peritumoral edema, remains debated. This study aimed to compare the clinical outcomes and toxicities in GBM patients treated with radiotherapy that includes or excludes peritumoral edema in the CTV.

Methods: This quasi-experimental, non-randomized prospective study was conducted over 12 months at the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Dhaka. Sixty postoperative GBM patients were enrolled and divided into two arms: Arm A (CTV including peritumoral edema) and Arm B (CTV excluding peritumoral edema). Clinical outcomes, including treatment response and toxicities, were assessed at 6 weeks and 6 months post-treatment.

Results: The baseline characteristics were well-matched between the two arms. At 6 weeks, the complete response (CR) rates were comparable between the two arms, with no significant difference. After 6 months, CR rates remained similar between Arm A (60.0%) and Arm B (53.3%), with no significant difference. However, Arm A exhibited significantly higher rates of toxicities, including nausea, vomiting, and headaches. Arm B showed lower toxicity levels, with fewer cases of severe vomiting and headaches.

Conclusion: The exclusion of peritumoral edema from the CTV results in similar tumor control compared to its inclusion, but with significantly lower toxicity levels. These findings suggest that excluding peritumoral edema from the CTV may be a preferable strategy for postoperative GBM management, offering comparable efficacy with reduced side effects.

Keywords: Glioblastoma Multiforme, Radiotherapy, Peritumoral Edema, Clinical Target Volume, Neurological Improvement

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Introduction

Glioblastoma Multiforme (GBM) is the most common and aggressive malignant primary brain tumor. Despite advancements in treatment, the prognosis for patients with GBM remains poor, with a median survival of less than two years [1]. The incidence of GBM ranges from 0.59 to 5 per 100,000 persons globally and is increasing in many regions. This rise in incidence is attributed to a combination of factors, including an aging population, overdiagnosis, exposure to ionizing radiation, and environmental factors such as air pollution [2]. GBM, along with other gliomas, is believed to originate from neuroglial progenitor cells. The 2016 revision of the World Health Organization (WHO) classification of central nervous system (CNS) tumors incorporated molecular features alongside histopathological characteristics, significantly advancing the classification of gliomas [3]. A crucial aspect of this revision for GBM diagnosis is the determination of isocitrate dehydrogenase (IDH) mutation status, which delineates distinct subgroups: GBM, IDH-wild-type; GBM, IDH-

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mutant; and GBM, not otherwise specified, the latter being reserved for cases where full IDH evaluation is not possible. Clinically, GBM can be categorized into primary and secondary types. Primary GBMs arise de novo without any clinical or histological evidence of a precursor lesion, whereas secondary GBMs progress from pre-existing lower-grade astrocytomas. Primary GBMs are characterized by genetic alterations such as epidermal growth factor receptor (EGFR) gene mutations and amplification, overexpression of mouse double minute 2 (MDM2), deletion of p16, and loss of heterozygosity (LOH) of chromosome 10q, which harbors the phosphatase and tensin homolog (PTEN) gene, as well as TERT promoter mutations [4]. Secondary GBMs, in contrast, commonly exhibit overexpression of platelet-derived growth factor A (PDGFA) and its receptor (PDGFRa), mutations in IDH1/2, TP53, ATRX, and LOH of 19q. Despite extensive research, the prognosis for GBM remains dire, underscoring the urgent need for more effective therapeutic strategies. Although significant efforts have been made in exploring immunotherapy and precision oncology, the unique biological characteristics of GBM, such as the blood-brain barrier and the tumor's microenvironment, present substantial challenges to the development of novel treatments [1]. The current standard treatment protocol for newly diagnosed GBM includes maximal safe surgical resection, followed by radiotherapy (RT) and concurrent adjuvant temozolomide (TMZ) chemotherapy [5]. However, the role of peritumoral edema as a prognostic factor in GBM patients remains controversial. For instance, Schoenegger et al. (2009) found that peritumoral edema on preoperative MRI was an independent prognostic factor for overall survival (OS) in GBM patients, alongside factors such as the postoperative Karnofsky Performance Score (KPS), age, and the type of tumor resection. Patients with major edema (>1 cm) exhibited significantly shorter OS compared to those with minor edema (<1 cm) [6]. Similarly, Pope et al. (2005) identified peritumoral edema, non-contrast-enhancing tumors, satellites, and multifocality as independent prognostic factors for survival in GBM, while tumor size, location, and extent of necrosis had no significant impact [7]. Conversely, Iliadis et al. (2012) reported no correlation between peritumoral edema, patient age, and tumor volume, but did observe an association between edema, tumor location, and necrosis [8].

Methods

The study was a quasi-experimental, non-randomized prospective design conducted over a period of twelve months from January 1st, 2020 to December 31st, 2020. The research was carried out at the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka. The study aimed to compare the outcomes and complications between target volumes with peritumoral edema and without peritumoral edema using conventional radiotherapy (RT) dose in a conformal technique with concurrent Temozolomide in patients with Glioblastoma Multiforme (GBM), WHO grade IV. The study population comprised patients with histopathologically proven GBM, WHO grade IV, who attended the Department of Radiation Oncology during the study period. A total of 60 patients were included in the study based on specific inclusion and exclusion criteria. Patients were selected through a purposive sampling technique. The inclusion criteria were patients aged between 18 and 70 years, with a Karnofsky performance status of 70 or above, histopathologically diagnosed GBM, WHO grade IV, and MRI-proven residual disease after surgery. Exclusion criteria included patients who had previously undergone brain radiotherapy, those with medical contraindications to Temozolomide, major vital organ dysfunctions such as kidney or heart disease, unwillingness to participate, or participation in any other clinical trial. Eligible patients were enrolled in the study after providing informed written consent. They were briefed on the objectives of the study, potential risks and benefits, their freedom to participate, and the confidentiality of their data. Data collection involved detailed medical histories, general examinations, and investigations, including computed tomography (CT) and/or magnetic resonance imaging (MRI). The 60 patients were divided into two arms of 30 patients each. Arm A received radiotherapy with a clinical target volume (CTV) that included the postoperative peritumoral edema as visualized on FLAIR/T2-weighted MRI plus a 2-2.5 cm margin. Arm B received radiotherapy with a CTV that included the postoperative residual tumor and cavity volumes on CT/T1-weighted MRI plus a 2-2.5 cm margin. In both arms, an additional 0.3-0.5 cm margin was added to the planning target volume (PTV). RT planning was performed using a conformal technique. Both arms also received concurrent Temozolomide at a dose of 75 mg/

m^2 continuously during the radiotherapy period, followed by a monthly dose of 150-200 mg/m^2 on a schedule of 5 days every 28 days for 6 cycles. During radiotherapy, patients were regularly assessed for treatment response and toxicities. Treatment response was evaluated using the RECIST criteria, and toxicities were observed using the RTOG acute radiation morbidity criteria.

Results

The majority of participants in both arms were aged 55-64 years (60.0% in Arm A, 53.3% in Arm B) and predominantly male (76.7% in Arm A, 80.0% in Arm B). Most were illiterate (63.3% in Arm A, 60.0% in Arm B), with a small percentage having completed SSC or equivalent education. A larger proportion lived in urban areas (63.3% in Arm A, 56.6% in Arm B). None of these differences were statistically significant.

Headache was the most common symptom, affecting 80.0% of participants in Arm A and 90.0% in Arm B. Nausea and vomiting were also frequent (60.0% in Arm A, 50.0% in Arm B), followed by seizures (43.3% in Arm A, 40.0% in Arm B). Neurological findings were similar across arms, with focal neural deficits observed in 33.3% of Arm A and 40.0% of Arm B participants. A significant portion of participants (43.3% in Arm A, 46.6% in Arm B) showed no neurological findings. None of these differences were statistically significant.

All participants in both arms (100%) exhibited hypointense lesions on T1-weighted MR scans and central areas of necrosis surrounded by white matter edema. A unifocal rim-enhancing mass in the parietal lobe was identified in 60.0% of Arm A and 66.7% of Arm B participants. Unifocal irregularly enhancing masses were found in 23.3% of Arm A and 20.0% of Arm B participants, while well-circumscribed homogeneously enhancing masses in the frontal lobe were seen in 16.7% of Arm A and 13.3% of Arm B participants. No statistically significant differences were observed between the two study arms.

Table-I

Distribution of baseline characteristics among the participants (N=60)

Variables n (%)	Arm A n (%)	Arm B	p-value
Age			
35-44	2 (6.6)	1 (3.3)	0.935
45-54	5 (16.6)	7 (23.3)	
55-64	18 (60.0)	16 (53.3)	
>64	5 (16.6)	6 (20.0)	
Gender			
Male	23 (76.7)	24 (80.0)	0.84
Female	7 (23.3)	6 (20.0)	
Education			
Illiterate	19 (63.3)	18 (60.0)	0.492
Below SSC	10 (33.3)	9 (30.0)	
SSC	1 (3.3)	3 (10.0)	
Residence			
Rural	11(36.6%)	13(43.3%)	0.72
Urban	19(63.3%)	17(56.6%)	

Table-II

Distribution of clinical manifestations amongst the respondents (N=60)

Variables	Arm An=30 n (%)	Arm Bn=30 n (%)	p-value
Clinical symptoms			
Headache	24 (80.0)	27 (90.0)	0.188
Seizure	13 (43.3)	12 (40.0)	0.861
Nausea, vomiting	18 (60.0)	15 (50.0)	0.502
Disorientation	8 (26.6)	7 (23.3)	0.227
Visual disturbance	7 (23.3)	2 (6.6)	0.743
Altered Consciousness	6 (20.0)	5 (16.6)	0.605
Anorexia	16 (53.3)	14 (46.6)	0.717
Neurological findings			
Focal neural deficit	10 (33.3)	12 (40.0)	0.302
Gait abnormality	8 (26.6)	8 (26.6)	0.618
Limb ataxia	4 (13.3)	3 (10.0)	0.109
Hemianopia	5 (16.6)	6 (20.0)	0.421
Cranial nerve palsy	9 (30.0)	8 (26.6)	0.381
Reflex asymmetry	6 (20.0)	4 (13.3)	0.121
None	13 (43.3)	14 (46.6)	0.392

Table-III

Distribution of MRI scan findings among the participants (N=60)

MRI Scans	Arm An=30 n (%)	Arm Bn=30 n (%)	p-value
Hypointense lesions on T1–weighted MR scans	30 (100.0)	30 (100.0)	1
Unifocal rim-enhancing mass in parietal lobe (right/ left)	18 (60.0)	20 (66.7)	0.109
Unifocal irregularly enhancing mass	7 (23.3)	6 (20.0)	0.272
Well-circumscribed homogeneously enhancing mass in frontal lobe (right/left)	5 (16.7)	4 (13.3)	0.113
Central area of necrosis, surrounded by white matter edema	30 (100.0)	30 (100.0)	1

None of the participants in either arm had a KPS of 90. A KPS of 80 was observed in 23.3% of participants in Arm A and 20.0% in Arm B. The majority of participants in both arms had a KPS of 70, with 50.0% in Arm A and 56.6% in Arm B. A KPS of 60 was reported in 26.6% of participants in Arm A and 23.3% in Arm B. These results indicate that the functional status of the participants, as measured by the KPS, was comparable between the two study arms, with no significant differences in their baseline performance status.

The hematological profile findings among the participants were assessed at different timeframes, and the results showed some significant differences between Arm A and Arm B. Hemoglobin levels (Hb%) were similar between the two arms at the 2nd week and 4th week, with no significant differences (p=0.109 and p=0.156, respectively). However, by the 3rd month, a significant difference was observed, with Arm B showing higher mean Hb% (12.57 ± 2.67) compared to Arm A (12.42 ± 1.09) (p=0.009). This difference became more pronounced after 5 months, where Arm B maintained a higher Hb% (12.78 ± 2.73) compared to Arm A (12.35 ± 2.4) (p=0.001). For the erythrocyte sedimentation rate (ESR), no significant differences were noted at any timeframe between the two arms. The mean ESR at the 2nd week was slightly higher in Arm A (121 ±

13.3) compared to Arm B (104 ± 17.1), but this difference was not statistically significant (p=0.211). Similar patterns were observed after 4 weeks, 3 months, and 5 months, with no significant differences between the groups. The total count of white blood cells (WBC) also showed no significant differences between the two arms across all timeframes. Although the WBC count was higher in Arm B at the 2nd week (14521.1 ± 875.1) compared to Arm A (13043.9 ± 964.2), this difference was not statistically significant (p=0.223). The WBC counts gradually decreased in both arms over time, with no significant differences observed at the 4th week, 3rd month, and 5th month.

At the 6th week of concurrent chemoradiotherapy (CCRT), the complete response (CR) rates were similar between the two groups, with 36.6% in Arm A and 30.0% in Arm B, showing no statistically significant difference (p>0.05). Partial response (PR) was observed in 30.0% of patients in Arm A and 40.0% in Arm B, while stable disease was reported in 20.0% of Arm B patients and none in Arm A. Progressive disease (PD) was slightly higher in Arm A (13.3%) compared to Arm B (10.0%). After 6 months of follow-up, CR rates remained comparable between the arms, with 60.0% in Arm A and 53.3% in Arm B, and no significant difference was observed (p>0.05). PR rates were also similar, with 23.3%

Table-IV

Distribution of karnofsky performance score (KPS) status among the participants (N=60)

Karnofsky performance score	Arm An=30 n (%)	Arm Bn=30 n (%)	p-value
KPS 90	0 (0.0)	0 (0.0)	0.275
KPS 80	7 (23.3)	6 (20.0)	
KPS 70	15 (50.0)	17 (56.6)	
KPS 60	8 (26.6)	7 (23.3)	

Table-V

Distribution of hematological profile findings at different timeframes among the participants (N=60)

Parameters	Arm An=30		Arm Bn=30		p value
	mean	± SD	mean	± SD	
Hb% (gm/dl)					
At 2nd week	11.1	0.75	11.4	0.89	0.109
After 4 weeks	11.86	1.23	12.13	1.23	0.156
After 3 months	12.42	1.09	12.57	2.67	0.009
After 5 months	12.35	2.4	12.78	2.73	0.001
ESR (mm in 1st hour)					
At 2nd week	121	13.3	104	17.1	0.211
After 4 weeks	94	18.5	97	12.4	0.247
After 3 months	82	24.7	92	19.1	0.183
After 5 months	87	16.6	86	11.5	0.265
TC of WBC					
At 2nd week	13043.9	964.2	14521.1	875.1	0.223
After 4 weeks	14380.2	1042.2	9892.8	856.4	0.174
After 3 months	9239.1	713.5	8592.5	786.1	0.289
After 5 months	7542.8	757.2	6542.8	423.7	0.307

in Arm A and 26.7% in Arm B. Stable disease was slightly higher in Arm B (10.0%) than in Arm A (6.7%), while PD rates remained equal in both arms at 10.0%.

In terms of radiotherapy-related toxicities, nausea was significantly more common in Arm A (73.3%) compared to Arm B (33.3%) ($p<0.05$), while Arm B had a higher proportion of patients without nausea (66.7% vs. 26.7%). Vomiting was more severe in Arm A, with 36.7% of patients experiencing Grade III vomiting compared to only 3.3% in Arm B ($p<0.01$), and Arm B had more patients with Grade I vomiting (60.0% vs. 26.7%). Skin reactions showed no significant differences between the arms, with most patients experiencing Grade I or II reactions in both groups. Anemia rates were similar between the two arms, with no significant differences in severity. Neutropenia was also comparable between the arms, with the majority of patients experiencing Grade II neutropenia, and no significant difference in severity. Headaches were significantly more frequent in Arm A (66.7%) compared to Arm B (33.3%) ($p<0.01$). Vertigo was more prevalent in Arm A (60.0%) than in Arm B (36.7%) ($p<0.001$). Altered levels of consciousness and memory loss were reported at similar rates in both arms, with no statistically significant differences.

Table-VI

Distribution of clinical response among the participants at different timeframes (N=60)

Clinical Response	Arm A n (%)	Arm B n (%)	p-value
At 6th week of CCRT			
Complete response (CR)	11 (36.6)	9 (30.0)	>0.05
Partial response (PR)	9 (30.0)	12 (40.0)	
Stable Disease	6 (0.0)	6 (20.0)	
Progressive disease (PD)	4 (13.3)	3 (10.0)	
After 6 months following treatment			
Complete response (CR)	16 (60.0)	16 (53.3)	>0.05
Partial response (PR)	7 (23.3)	8 (26.7)	
Stable Disease	2 (6.7)	3 (10.0)	
Progressive disease (PD)	3 (10.0)	3 (10.0)	

Table-VII

Distribution of radiotherapy related toxicities among the participants (N=60)

Toxicity n (%)	Arm A n (%)	Arm B	p-value
Nausea			
Present	22 (73.3)	10 (33.3)	<0.05
Absent	8 (26.7)	20 (66.7)	
Vomiting			
No	3 (10.0)	7 (23.3)	<0.01
Grade I	8 (26.7)	18 (60.0)	
Grade II	8 (26.7)	4 (13.3)	
Grade III	11 (36.7)	1 (3.3)	
Skin Reaction			
Grade I	14 (46.7)	17 (56.7)	>0.05
Grade II	12 (40.0)	10 (3.3)	
Grade III	4(13.3)	3 (10.0)	
Anemia			
No	13 (43.3)	17 (56.7)	>0.05
Grade I	12 (40.0)	9 (30.0)	
Grade II	5 (16.7)	4 (13.3)	
Neutropenia			
No	9 (30.0)	11 (36.7)	>0.05
Grade I	5 (16.7)	5 (16.7)	
Grade II	12 (40.0)	11 (36.7)	
Grade III	4 (14.7)	3 (10.0)	
Headache			
Present	20 (66.7)	10 (33.3)	<0.01
Absent	10 (33.3)	20 (66.7)	
Vertigo			
Present	18 (60.0)	11 (36.7)	<0.001
Absent	12 (40.0)	19 (63.3)	
Altered level of consciousness			
Present	18 (60.0)	14 (46.7)	>0.05
Absent	12 (40.0)	16 (53.3)	
Loss of memory			
Present	12 (40.0)	16 (53.3)	>0.05
Absent	18 (60.0)	14 (46.7)	

Discussion

The present study aimed to compare the outcomes of radiotherapy target volume delineation with and without peritumoral edema in patients with postoperative Glioblastoma Multiforme (GBM). This quasi-experimental study enrolled 60 patients with histopathologically confirmed GBM and investigated the impact of including peritumoral edema in the clinical target volume (CTV) on clinical outcomes, including

neurological improvement and treatment response. The baseline characteristics of the participants, including age, gender, education, and residence, were well-matched between the two study arms, with no statistically significant differences. This comparability in baseline characteristics ensures that the observed differences in outcomes are likely attributable to the treatment strategies rather than demographic variations. The importance of well-matched baseline characteristics has been highlighted in similar studies, such as those by Thakkar et al., who underscored the significance of controlling for confounding factors in GBM research to ensure valid comparisons between treatment groups [9]. Clinically, headache was the most prevalent symptom among participants, reported by 80.0% in Arm A and 90.0% in Arm B, consistent with findings from other GBM studies that highlight headache as a common presenting symptom due to increased intracranial pressure [10]. Additionally, neurological findings revealed that focal neural deficits were present in 33.3% of participants in Arm A and 40.0% in Arm B. These findings align with previous studies indicating that neurological deficits, such as motor weakness and sensory disturbances, are frequent in GBM patients due to the tumor's location and invasion of adjacent brain structures [11]. The MRI scan findings were consistent across both study arms, with all participants exhibiting hypointense lesions on T1-weighted MR scans and a central area of necrosis surrounded by white matter edema. This observation is in line with established imaging characteristics of GBM, where central necrosis and peritumoral edema are hallmark features [12]. The inclusion of peritumoral edema in the CTV is a debated topic, with studies such as those by Pope et al. demonstrating that peritumoral edema can be a significant prognostic factor, potentially influencing overall survival and treatment outcomes [7]. Karnofsky Performance Score (KPS) at baseline was also comparable between the two arms, with a majority of participants having a KPS of 70, indicating a relatively preserved functional status at the start of the study. The KPS is a critical prognostic tool in GBM, as shown in studies by Ciammella et al., where KPS was a strong predictor of survival outcomes, further emphasizing the need to account for baseline functional status in clinical trials [13]. Hematological profile assessment revealed significantly higher hemoglobin levels in Arm B at both 3- and 5-months post-treatment compared to Arm A. While the exact cause of this difference is unclear, it may be related to variations in treatment-related hematological toxicity or patient response to concurrent therapies. Previous research has demonstrated that higher hemoglobin levels can be associated with better treatment tolerance and outcomes in GBM patients, as noted by Fiorentino & Fusco [14]. However, the lack of significant differences in other hematological parameters suggests that both treatment approaches had comparable safety profiles. Radiotherapy-related toxicities, such as nausea, vomiting, and headaches, were significantly more common in Arm A compared to Arm B. Nausea was present in 73.3% of participants in Arm A versus 33.3% in Arm B ($p<0.05$), and vomiting was more severe in Arm A, with 36.7% of participants experiencing Grade III vomiting compared to 3.3% in Arm B ($p<0.01$). Headaches were also significantly more frequent in Arm A (66.7%) than in Arm B (33.3%) ($p<0.01$). These findings suggest that including peritumoral edema in the CTV may be associated with higher toxicity rates. These findings are consistent with other studies, where similar toxicity profiles have been observed in GBM patients undergoing radiotherapy, particularly when combined with temozolomide [15]. Niewald et al. reported comparable findings, noting that the addition of temozolomide to radiotherapy did not significantly increase the incidence of severe toxicities but did improve survival outcomes [16]. The clinical response, assessed at both 6 weeks and 6 months post-treatment, showed no significant difference in complete response (CR) rates between the two arms at 6 months, with 60.0% in Arm A and 53.3% in Arm B ($p>0.05$). Similarly, partial response (PR) rates were comparable between the arms, with 23.3% in Arm A and 26.7% in Arm B. These updated findings indicate that excluding peritumoral edema from the CTV does not necessarily result in superior tumor control compared to including it. This finding is supported by studies such as those by Cozzi et al., which demonstrated that specific radiotherapy approaches could enhance tumor response and improve survival rates in GBM patients [17]. In conclusion, this study highlights the potential advantages of excluding peritumoral edema from the CTV in terms of clinical response, while including edema may benefit neurological outcomes. These findings contribute to the ongoing debate about the optimal approach to

radiotherapy target volume delineation in GBM and underscore the importance of personalized treatment strategies. Further research, ideally through randomized controlled trials, is needed to validate these findings and refine radiotherapy protocols for GBM patients.

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

Conclusion

The present study concludes that the clinical response to radiotherapy using a target volume that excludes peritumoral edema is comparable to that of radiotherapy including peritumoral edema for the treatment of postoperative Glioblastoma Multiforme. However, radiotherapy without peritumoral edema is associated with significantly lower toxicity levels. Therefore, excluding peritumoral edema from the radiotherapy target volume may be a preferable option for treating postoperative Glioblastoma Multiforme, offering similar efficacy with reduced side effects.

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