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Original Article

Biological Dose Escalation—Do We Have a New Window of Opportunity in High-Grade Glioma? —A Feasibility Study

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Abstract

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Despite multimodality treatment in high-grade glioma (HGG) involving maximal safe resection and adjuvant chemoradiotherapy, the prognosis remains dismal. In this study, we aimed to evaluate a method of biological enhancement by combining dose escalation with a condensed overall treatment time, aiming for maximal cytoreduction as a surrogate for improved outcomes. Hypofractionation has the dual advantage of enhanced cell kill with reduced overall treatment time. To this effect, we have employed a study involving hypofractionated simultaneous integrated boost (SIB) versus conventional treatment. As a secondary objective, we evaluated volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy (IMRT) in terms of optimal delivery technique for SIB boost. Forty patients were randomized into two arms, the study arm received 60 Gy in 25 fractions and the standard arm received 60 Gy in 30 fractions with concurrent and adjuvant temozolomide. The patients were assessed radiologically for tumor cytoreduction and acute toxicity parameters weekly during treatment, 6 weeks post-treatment, and 3 monthly follow-up. All patients were planned using VMAT and IMRT techniques in the study arm for the comparison of treatment time and dosimetric efficiency. However, the treatment was performed through VMAT technique. Data were analyzed using simple descriptive statistics including Student's *t*-tests, proportion tests, and Pearson correlation for association. The total sample size was estimated at 40, with 20 samples per group, providing a statistical power of 81% and a significance level (*p*-value) of 0.05. It was observed that tumor cytoreduction was significantly enhanced in a subgroup of patients in the study arm with smaller volume residual disease ($p = 0.04$) that was found at 6 weeks post-treatment evaluation. The tolerance, toxicity, and compliance were comparable in both arms. During the dosimetric evaluation, it was determined that VMAT had a significantly lower hot spot compared to the IMRT plan (64.22 Gy vs. 64.75 Gy, $p = 0.02$). It was also observed that the delivery with VMAT was faster and involved a lesser number of monitor units (555.7 MU vs. 679.6MU, $p = 0.001$). The hypofractionated SIB

Keywords

- gliomas
- hypofractionation
- SIB
- VMAT
- IMRT

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radiotherapy using the VMAT technique can provide a feasible method of biological dose enhancement without compromising toxicity and might have the future potential to improve local control in HGG.

Introduction

Central nervous system tumors account for 3% of all malignancies.[1] They are responsible for considerable morbidity and mortality worldwide with increasing incidence over the years.[2] The death rate has been decreasing over time with the 5-year relative survival rate for primary brain tumors improving from 24% during 1975 through 1977 to 35% during 1996 through 2003.[1] This improvement in survival statistics can be attributed to the incorporation of concurrent and adjuvant chemotherapy as a radiosensitizer as well as more localized tumor directed treatment. This shows that enhancement of local treatment improves local control and has a potential for improving survival that opens up the scope for further exploring this venue. However, the overall survival of patients with high-grade glioma remains poor even with multimodality treatment. The median survival of patients with glioblastoma (GBM) is 14.2 months.[3] It is in this context that radiobiologically manipulated fractionation may help us to improve the local control further with subsequent benefit on disease-free survival and potential improvement of overall survival. The most effective radiobiological potentiation of radiation effect in the current era is localized integrated hypofractionation with simultaneous integrated boost (HFRT-SIB) allowing for a reduction of overall treatment time. It is this concept that we have tested in our study.

One hypothesis for poorer outcomes following the use of a protracted radiation schedule can be from tumor repopulation of GBM and anaplastic gliomas which notably have a rapid doubling time. Approximately 12 to 37.5% of patients have been observed to progress during or toward the end of a conventionally fractionated radiation schedule.[4] One important biological intervention that has been evaluated to counter this is the use of HFRT. HFRT has the dual advantage of achieving increased cell kill from the higher dose per fraction and reducing the effect of accelerated repopulation by shortening overall treatment time. However, this potential benefit is masked by the risk of enhanced toxicity of the normal neural tissue. The initial studies of hypofractionated treatment schedules were directed toward reducing overall treatment time in a subgroup of poor prognosis patients. However, the survival statistics of these studies evidenced noninferiority as well as acceptable toxicity.[5,6] In the last few decades, the advent of higher precision radiation delivery systems and techniques has provided the means to achieve the dual goal of focused HFRT and relative sparing potentially feasible. Intensity modulated radiotherapy (IMRT) with simultaneous integrated boost is one such technique that is being evaluated in this context. Among available techniques, volumetric modulated arc therapy (VMAT) has some clinical data to suggest a few advantages over IMRT.[7] It has the scope of better coverage, lower mean brain dose, and involves less number of monitor units (MU) and treatment time.[8] In a disease with a dismal prognosis, the shorter overall treatment time is an especially attractive option from the patient's perspective as well.

The primary objective of this study was to compare volumetric cytoreduction achieved with HFRT-SIB protocol versus conventional radiotherapy. Other end-points that were evaluated were tolerance, toxicity, and compliance with the HFRT-SIB protocol. We also evaluated which technique would have a dosimetric superiority in delivering the SIB protocol.

Materials and Methods

This was a randomized open-labeled observational study approved by the Clinical Ethics Board. The random allocation was made using computer-designed random numbers. The study was proposed to evaluate 40 patients to be randomized into the study arm to receive 60 Gy in 25 fractions and the control arm to receive 60 Gy in 30 fractions. All patients received treatment via VMAT plan with concurrent temozolomide 75 mg/m2 followed by adjuvant temozolomide of 150 mg/m2 first cycle and 200 mg/m2 for the subsequent 5 cycles in both arms.

Inclusion Criteria

The inclusion criteria of the current study were as follows:

- Patients with high-grade glioma that have undergone decompression of their primary disease and require adjuvant chemo irradiation.
- Patients with more than 1 cm residual disease documented on postoperative magnetic resonance imaging (MRI).

Exclusion Criteria

- Patients with more than 5 cms residual disease on postoperative MRI.
- Patients with uncontrolled comorbidities.

All patients fulfilling the inclusion criteria registered in the Department of Radiation Oncology, Kidwai Memorial Institute of Oncology, Bengaluru from November 2019, to August 2021, were taken in the study. Patient parameters including age, sex, tumor site, histology, comorbidities, details of the surgery, and preoperative imaging details were recorded. Written informed consent was taken from all patients who took part in the study.

Patients underwent computed tomography (CT) simulation from vertex to inferior border of C3 vertebrae with 3mm slice thickness on a Philips large bore CT (Philips Medical Systems, Cleveland, Ohio, United States) simulator scanner.

Patients in group A (SIB HFRT protocol) were contoured with two planning volumes of planning target volume (PTV) 60/25 and PTV 50/25. Gross tumor volume (GTV) included the resection cavity plus any residual enhancing tumor on contrast-enhanced T1-weighted MRI. Clinical target volume (CTV) was defined as GTV plus 2 cm in all directions to account for the microscopic spread. PTV 60/25 included GTV + 5 mm and PTV 50/25 included CTV + 5 mm. Patients in group B (standard fractionation) received treatment as per European Organisation for Research and Treatment of Cancer (EORTC) guidelines-single treatment volume. CTV 60/30 included GTV + 2 cm and PTV 60/30 included CTV60 + 5mm. The organ at risk (OAR) was contoured according to the OAR contouring atlas. Patients were planned with Monaco treatment planning systems version:5.11.02 and treated on an Elekta Infinity/Versa HD machine.

In the study group, all the patients were planned with VMAT SIB and received 60 Gy in 25 fractions, 5 fractions a week, over 5 weeks. Both IMRT and VMAT plans were generated for all patients in the study arm for dosimetric comparison of tumor coverage and normal tissue sparing. In the control group, all patients were planned with VMAT and received 60 Gy in 30 fractions and 5 fractions a week over 6 weeks. All patients received concurrent temozolomide as a daily dose of 75 mg/m2 for 7 days a week and adjuvant chemotherapy of 150 mg/m2 for 6 cycles.

The planning objectives were as follows: PTV 95% volume should receive 95% of the dose for both PTV 60 and PTV 50. The maximum dose (Dmax) for the PTV should be less than 107%.

►Table 1 shows the dosimetric constraints applied.

Assessment of Primary and Secondary Objectives

Patients in both arms underwent a planned volumetric radiological assessment of tumor cytoreduction at pre-planned intervals with a simulation CT. The planned intervals for the same were at 13 fractions and 6 weeks post-treatment. Patients also underwent a T1 contrast and T2 Flair MRI brain 6 weeks and 3 months post-treatment for response evaluation. Subsequently, patients were followed up with MRI at 3-month intervals. The patients were evaluated for acute toxicity related to nausea, fatigue, headache, and alopecia according to Common Terminology Criteria for Adverse Events (CTCAE) v5 (31) grading at baseline, every week during treatment, 6 weeks post-treatment, and 3 months post-treatment. All patients received treatment by VMAT technique in both arms.

Table 1 Dosimetric constraints

Organ at risk	Constraints (Gy)
Optic nerve Dmax	< 54
Eye Dmax	<45
Lens Dmax	<10
Brainstem Dmax	< 54
Optic chiasm Dmax	< 54

Abbreviation: Dmax, maximum dose.

As the secondary objective, two plans were generated for each patient in the protocol arm using VMAT and IMRT techniques. The dosimetric parameters compared were PTV 95% coverage, Dmax to PTV, conformity index, homogeneity index, and dose to the OAR. As a second objective, the normal tissue dose constraints of the above-mentioned OARs were compared between the VMAT plans of the study arm and control arm.

Statistical Methods

Descriptive and inferential statistical analysis has been performed in the present study. This was performed using the Student's *t*-test. Descriptive statistics of categorical variables were reported in total numbers and percentages. Continuous variables were reported as mean, median, and standard deviation. Pearson's correlation was used to find out association. The Statistical Software namely SPSS 22.0 was used for the analysis of the data. The sample size was calculated using the G Power Software V.3.9.7. The total sample size was estimated at 40 (20 samples per group) with a power of 81%. A *p*-value of less than 0.05 was considered statistically significant.

Results

Pretreatment Characteristics

In this study, we have evaluated gender, grade of tumor, isocitrate dehydrogenase (IDH) status, the extent of resection, and steroid dependence as the baseline characteristics.

As seen in ►Table 2, the baseline characteristics in the two groups were significantly similar. All 20 (100%) patients in the

Table 2 Patient characteristics

Gender	Study	Control
Male	11 (55%)	11 (55%)
Female	9 (45%)	9 (45%)
Grade		
III	10 (50%)	12 (60%)
IV	10 (50%)	8 (40%)
IDH status		
Positive	12 (60%)	14 (70%)
Negative	8 (40%)	6 (30%)
Comorbidities		
Nil	16 (80%)	15 (75%)
Present	4 (20%)	5 (25%)
Extent of resection		
Near-total resection	7 (35%)	11 (55%)
Subtotal resection	4 (20%)	7 (35%)
Partial resection	9 (45%)	2 (10%)
Steroid dependance		
Nil	17 (85%)	15 (75%)
Yes	3 (15%)	5 (25%)

Abbreviation: IDH, isocitrate dehydrogenase.

study arm and control arm were able to complete the planned radiation dose of 60 Gy in 25 fractions and 60 Gy in 30 fractions, respectively, without any treatment breaks showing 100% compliance. All patients in both arms received concurrent temozolomide of 75mg/m^2 7 days a week followed by adjuvant temozolomide 150 mg/m^2 in the first cycle followed by 200 mg/m^2 for the remaining five cycles over 6 months.

Disease Characteristics

Both protocol and control arm were comparable in terms of tumor histology, disease characteristics, and steroid dependence. There were 10 (50%) patients with grade III glioma in the study arm compared with 12(60%) patients in the control arm. IDH mutation was seen in 12 (60%) patients in the study arm that was similar to 14(70%) patients in the control arm. All patients had postoperative MRI showing residual disease measuring between 1 and 5 cm in size. The extent of resection in the study arm was as follows seven patients (35%) underwent near-total resection, four patients (20%) underwent subtotal resection, and nine patients (45%) underwent partial resection. In the study arm, 11(55%), 7(35%), and 2 (10%) patients underwent near-total, subtotal, and partial resection, respectively. Only three (15%) and five (25%) patients received steroids during treatment in the study arm and control arm, respectively.

Comparative Volumetric Cytoreduction

Patients were evaluated for volumetric cytoreduction (of GTV) at mid-treatment and 6 weeks subsequently. It was observed that the protocol arm had a trend toward enhanced cytoreduction that was apparent at 6 weeks evaluation of response (►Fig. 1). The protocol arm showed a statistically significant inverse correlation between residual tumor volume and cytoreduction ($p = 0.004$). A smaller residual tumor volume appeared to benefit more from a higher dose per fraction. A tumor volume of 20 cc was taken as a cutoff for statistical evaluation of cytoreduction. Patients with smaller tumor volume (<20cc) showed better cytoreduction in terms of GTV at 6 weeks post-treatment compared with larger tumor volume. The correlation between tumor cytoreduction and residual tumor volume for the control arm was not found to be statistically significant ($p = 0.09$; ►Fig. 2).

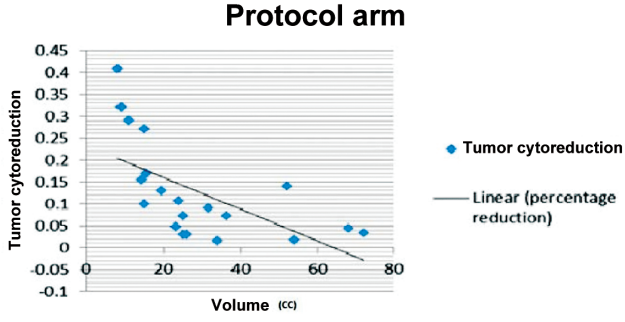

Fig. 1 Correlation between tumor cytoreduction and residual tumor volume in the protocol arm. The above graph shows the correlation between tumor cytoreduction and residual tumor volume in the protocol arm. The volume was evaluated in terms of a cubic centimeter(cc) and tumor volume of 20cc was taken as the cutoff for statistical evaluation of cytoreduction.

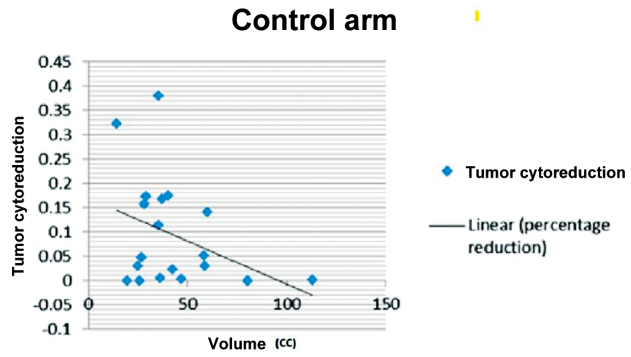

Fig. 2 Correlation between tumor cytoreduction and residual tumor volume in the control arm. The above graph shows the correlation between tumor cytoreduction and residual tumor volume in the control arm. Similar statistical evaluation in the control arm shows no correlation of cytoreduction with tumor volume.

This shows that with conventional fractionation the response to treatment was independent of the tumor volume. From this, we can probably infer that HFRT is more effective for smaller tumor volumes and this may be a significant indicator of which patients might benefit from the same.

Evaluation of Toxicity Parameters

Toxicity of the brain was assessed by CTCAE version 5.0. In the protocol arm, six patients (30%) had grade 1 alopecia, one patient (5%) had grade 1 headache, three patients (15%) had grade 2 headache, and grade 2 vomiting requiring steroid administration. In the control arm, five patients (25%) had grade 1 alopecia, two patients (10%) had grade 1 headache, three patients (15%) had grade 2 headache, and grade 2 vomiting requiring steroid administration. All patients in both arms completed treatment within the given overall treatment time. No grade 3 or grade 4 toxicities were noted in both arms.

Dosimetric Comparison of SIB Delivery Using VMAT vs IMRT

In our study, patients in both arms were treated with VMAT. However, as a secondary objective, each patient in the study arm was planned with VMAT and IMRT for comparison of the best delivery technique. The parameters evaluated were PTV coverage, homogeneity index, conformity index, the Dmax to PTV, MU, and dose to normal tissue. The normal tissue parameters evaluated were Dmax of the brainstem, Dmax of bilateral optic nerves, Dmax of the bilateral eye, Dmax of the optic chiasm, and mean dose to the brain.

The planning objective of our study was PTV 95% should receive 95% of the dose for both PTV 60 and PTV 50. The Dmax for the PTV should be less than 107%. The OAR doses were kept as low as possible and within the constraints given by Quantitative Analysis of Normal Tissue Effects In The Clinic (QUANTEC-2012) without compromise of tumor coverage.

VMAT had an edge over IMRT in terms of Dmax of PTV and MU. The mean Dmax of PTV in the VMAT plan was 64.22 and 64.75 Gy in the IMRT plan ($p = 0.02$). This hints that VMAT may be able to provide a more homogenous plan (►Fig. 3). The mean MU for the VMAT plan delivery was 555.7 MU

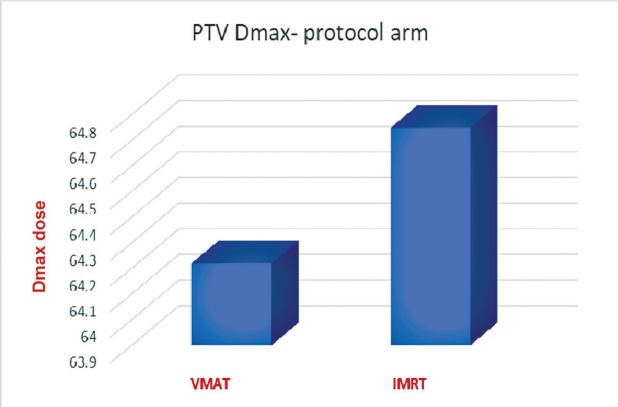

Fig. 3 Planning target volume (PTV) maximum dose (Dmax) in volumetric modulated arc therapy (VMAT) versus intensity modulated radiotherapy (IMRT) in the protocol arm. The above graph depicts the maximum dose of PTV in VMAT and IMRT plans of the hypofractionated simultaneous integrated boost treatment. There was a significant difference between the two with VMAT showing a more homogenous distribution. volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy (IMRT).

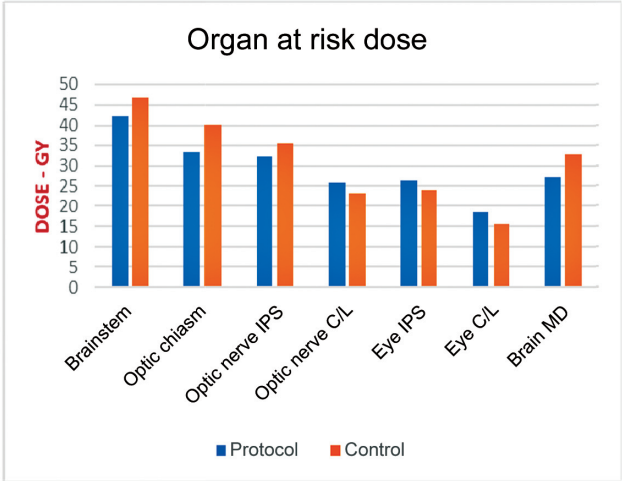

Fig. 5 Normal tissue sparing between the protocol and control arm. The above graph shows the mean dose of organ at risk (Gy) between the hypofractionation and conventional arm. The two plans were comparable in terms of normal tissue sparing as depicted above. This shows that hypofractionated simultaneous integrated boost is a feasible option for high-grade gliomas in terms of toxicity.

compared with 679.6 for the IMRT plan ($p = 0.001$; ►Fig. 4). This implied that the VMAT plan had an additional advantage of lesser MU and thus a shorter treatment time. This could potentially correlate with a biological advantage as well as less dose scatter and contamination. The normal tissue sparing was also evaluated between the VMAT plans of the hypofractionated SIB arm and conventional arm. The dose constraints to the above-mentioned OARs were comparable between the two VMAT plans (►Fig. 5). This clearly shows that hypofractionated radiotherapy with simultaneous integrated boost could be delivered with a comparable toxicity to conventional treatment.

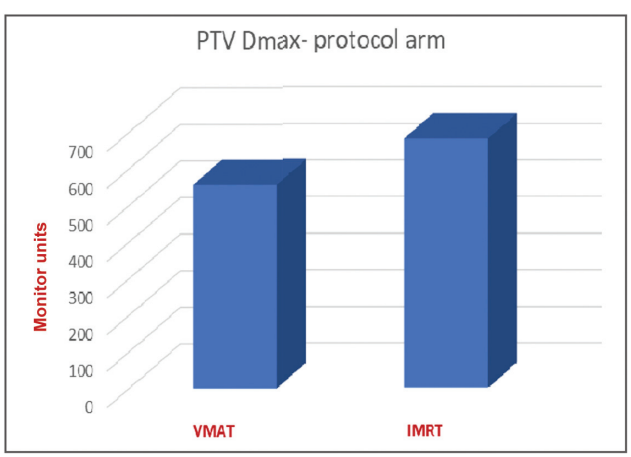

Fig. 4 Monitor units in volumetric modulated arc therapy (VMAT) versus intensity modulated radiotherapy (IMRT) in the protocol arm. The above graph depicts the monitor units involved in the delivery of VMAT and IMRT plans in the hypofractionated simultaneous integrated boost arm. A significant difference between the two was seen with the VMAT plan having lesser monitor units and hence a shorter treatment time. Dmax, maximum dose; PTV, planning target volume.

Discussion

The current standard of care in high-grade gliomas includes maximal resection of the tumor followed by adjuvant chemoradiotherapy with temozolomide over a period of 6 weeks.[3] The compromise in the outcome following the use of this protracted treatment schedule may be due to tumor repopulation and rapid doubling time in high-grade gliomas. This has led to further dose escalation studies using conventional and altered fractionation. Earlier studies of dose escalation using conventional fractionation up to 70Gy did not show any survival benefit.[9] It was postulated that prolonging treatment time was associated with accelerated repopulation of glioma cells thus reducing efficacy. Similarly, studies using HFRT were evaluated that again showed no specific benefit.[10] The other approach for dose escalation was using HFRT. This had the dual advantage of increased cell kill by higher dose per fraction and reducing the effect of accelerated repopulation by condensed overall treatment time. The initial studies of dose escalation by HFRT were directed toward a subgroup of poor prognostic elderly patients to reduce the overall treatment time. The survival studies evidenced noninferiority and acceptable toxicity.[11] In the last few decades, the advent of higher precision radiation delivery systems and techniques has provided the means to achieve the dual goal of focused HFRT and relative sparing potentially feasible. The advent of IMRT gives the advantage of simultaneous delivery of different doses per fraction within the target volume. This allows a higher BED to the tumor bed with the added advantage of reduced overall treatment time. A meta-analysis by Liao et al in 2019 evaluating the efficacy and safety of hypofractionated radiotherapy over conventional fractionation in GBM showed comparable overall survival ($p = 0.64$) and progression-free survival ($p = 0.79$) and similar rates of adverse events.[12] The

meta-analysis included 15 studies with doses ranging from a BED of 38 to 98 Gy. They also found that in patients aged more than 70 years there was higher overall survival with HFRT ($p = 0.02$). They concluded that HFRT is efficacious and safe for GBM and the role of the same in good prognostic factors requires further evaluation. The disadvantage of this study was that around 53% (8) studies in the meta-analysis used a BED less than 72 Gy (conventional fractionation). Since HFRT was found to be comparable in terms of efficacy and toxicity even with a lower BED, there appears to be a scope in exploring this concept with higher BEDs, and this was the focus of our study. In our study, we evaluated the potential for enhanced cytoreduction through biological manipulation of dose fractionation and delivery. The efficacy of this concept was tested through the volumetric cytoreduction of tumors during the course of radiotherapy and subsequently at 6 weeks post-treatment. For focused dose-escalation, we have incorporated a hypothesis of biological enhancement of not only higher dose per fraction but also the reduction of overall treatment time. The quantification of radiobiological benefit was done through serial radiological assessment and documentation of tumor cytoreduction. It was observed that radiotherapy arm showed a trend toward enhanced cytoreduction that was significant at 6 weeks post-treatment ($p = 0.004$). This was observed in patients with a smaller tumor volume of less than 20cc compared with larger volumes. The mean cytoreduction in tumor volume was more in the protocol arm compared with the control arm. Although this was not statistically significant, it is worth evaluating this in a larger cohort of patients. From this, we could infer that patients with favorable features who have good resection of the tumor with small- volume residual disease might potentially benefit from hypofractionated radiotherapy. Our results were consistent with studies evaluating the role of HFRT in high-grade glioma. A study by Scoccianti et al evaluating the role of hypofractionated radiotherapy with SIB plus temozolomide in 24 patients with a good prognosis (Recursive Partitioning Analysis [RPA] class III and IV) showed a median overall survival of 15.1 months and progression-free survival of 8.6 months. There was no radiotherapy-related acute toxicity or discontinuation of chemotherapy confirming that HFRT-SIB with temozolomide may be a reasonable and feasible option for good prognosis patients with GBM.[13] However, our study had the advantage of larger numbers and a comparative arm. We were also able to establish a subset of the patients that would benefit from hypofractionated radiotherapy. As we know HFRT causes a marginal increase in acute toxicity and a significantly larger increase in late toxicity. We wanted to evaluate the toxicity of our study arm to the conventional arm. The complete treatment was well tolerated in the study arm and comparable in terms of compliance and toxicity with the control arm receiving conventional treatment. There were no significant treatment breaks on account of toxicities and all patients were able to complete the protocol. No patients had grade 3 or grade 4 toxicity requiring interruption of treatment in both arms. These results were consistent with other similar studies evaluating efficacy and safety of HFRT in newly diagnosed high-grade glioma.[14]

From this, we can infer that HFRT with protracted treatment time is not more toxic than conventional fractionation and has potential for further evaluation especially in patients with favorable features and small residual tumors.

As our secondary objective, we evaluated the dosimetric factors including normal tissue doses between the hypofractionated arm and conventional arm with the intent of identifying the better delivery technique. In this endeavor, our secondary objective compared the VMAT plan between HFRT and conventional RT. A second objective involved a dosimetric comparison between IMRT and VMAT techniques in delivering the SIB hypofractionated treatment plan. In our study, we found no significant difference between normal tissue sparing in the protocol arm and control arm. This showed that hypofractionated SIB is a feasible and safe option for patients with high-grade glioma with the dual advantage of higher differential tumor dose and reduced treatment time with the potential of enhanced cytoreduction. On the evaluation of a better treatment technique for HFRT, we found that VMAT had an edge over IMRT in terms of Dmax to PTV (64.22 vs. 64.75 Gy, $p = 0.02$) and shorter delivery time in terms of MU (555.7 vs. 679.6 MU, $p = 0.001$). The high-dose region was limited in VMAT, although there was no significant difference in homogeneity index that was probably due to the smaller cohort of patients. The above results also show that VMAT had reduced treatment time. Reduced treatment time has an additional advantage in a high-volume center in allowing for more patients to be treated per day. There was no difference found between conformity index, homogeneity index, and dose to the normal tissue. However, other studies have shown some data that are different from ours and this could be due to the smaller sample size in our study.[15–18] Pragna et al in 2018 did a dosimetric comparison between IMRT and VMAT plan in 28 patients for glioma. Among the two plans, they found that IMRT had better PTV coverage at the expense of mean dose to the brain. ($p = 0.021$). The conformity index was also better in the IMRT plan ($p = 0.01$). The normal tissue dose of the ipsilateral optic nerve was inferior in the VMAT arm ($p = 0.02$). They also found that MU and treatment time were reduced in the VMAT plan ($p < 0.001$).[16,17] This particular study did not show any dosimetric advantage of VMAT over IMRT.

The limitations of our study include small sample size and short follow-up to evaluate the sustained clinical response and late toxicities including radionecrosis. The trial could be further validated by including treatment-related outcomes (local recurrence, progression-free survival, and overall survival) with effect on the quality of life and overall toxicity.

Conclusion

The hypofractionated simultaneous integrated boost (SIB) treatment using VMAT provides a radiobiologically sound, effective, and safe protocol that has the potential to improve the treatment of high-grade gliomas significantly so in small volume disease. The good tolerability and toxicity profile in

the study arm is encouraging and facilitates further research with this protocol.

Conflict of Interest

None declared.

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