

# Dosimetric Comparison between 6MV Flattened Filter and Flattening Filter Free Photon Beams in the Treatment of Glioblastoma with IMRT Technique: A Treatment Planning Study

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## ABSTRACT

**Introduction:** The present study evaluated the dosimetric comparison between 6MV flattened filter (FF) and flattening filter-free (FFF) photon beams in intensity-modulated radiation therapy (IMRT) technique for the treatment of glioblastoma (GBM) patients.

**Material and Methods:** The present study was conducted on 10 patients with GBM previously planned and treated with 6MV FF photon beam by IMRT technique. Additional IMRT plans were retrospectively created using 6MV FFF photon beam for each patient plan. The dose prescription, beam parameters, and planning objective were kept same in both plans. The plans were evaluated using cumulative dose-volume histogram (c-DVH). Both types of plans were compared on the basis of homogeneity index (HI), conformity index (CI), beam-on time (BOT), monitor unit (MU), and doses to organs at risk (OARs).

**Results:** Dose received by 95% ( $D_{95\%}$ ) of planning target volume (PTV) coverage was observed significantly higher in 6MV\_FF\_IMRT plan than 6MV\_FFF\_IMRT plan ( $P < 0.05$ ). No significant dose differences were noticed for HI, CI,  $D_{98\%}$ , and  $D_{2\%}$  between both plans. Significantly lower  $D_{max}$  for the brainstem, eyes, and eye lens was observed in 6MV\_FFF\_IMRT plan. For the brain, less than 2% mean dose was observed in 6MV\_FFF\_IMRT plan than 6MV\_FF\_IMRT plan ( $P = 0.017$ ). In 6MV\_FFF\_IMRT plan, mean BOT decreased by 39% in comparison to that in 6MV\_FF\_IMRT plans.

**Conclusion:** The 6MV FFF beam provides a desirable and clinically acceptable IMRT plan for the treatment of GBM than 6MV FF beam. In addition, 6MV FFF beam provides higher MUs, better OARs sparing, lower scattered dose, and lower beam delivery time.

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## Introduction

Glioblastoma (GBM) also known as GBM multiforme is among the most common cancers that begin within the brain. It is the most typical and harmful brain malignancy in adults. Signs and symptoms of GBM are indifferent; however, they may include headaches, personality changes, nausea, and symptoms more or less similar to those of stroke and obliviousness. The GBM is aggressive in nature and penetrates into the regions close to the brain. Performing surgery is the primary step in the treatment of GBM; however, the complete removal of tumor is not possible due to infiltration and diffusive nature of GBM.

Surgery alone can provide median survival level of only 3 to 4 months [1-3]. In the present practice, postoperative radiotherapy is the basic treatment for high-grade GBM. Results of several randomized

controlled trials have revealed that postoperative radiotherapy increases the mean survival time of patients from 3-6 to 9-12 months [4]. Intensity-modulated radiation therapy (IMRT) has been exhibited to yield a higher level of conformal dose distribution, compared to conventional radiotherapy with better sparing of neighboring healthy tissues [5, 6].

The primary goal in external beam radiotherapy treatment is to accurately deliver high-localized dose to the tumor while sparing the normal organs, which are closely situated to the tumor. Therefore, it is very important to limit the radiotherapy doses to normal organs in close proximity to the target area. Restriction of the doses to adjacent healthy tissues will be useful in curtailing the acute and late toxicity of the treatment. It has been observed that dose

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constraints of the neighboring healthy critical tissue are restricted to deliver the desired therapeutic dose to the target.

The IMRT treatment planning has gained the popularity among the available treatment techniques. The IMRT has been proved to save the normal tissue by keeping radiation doses well below their tolerance limit, along with better or similar treatment plan quality, compared to three-dimensional conformal radiation therapy [5-7]. According to the literature, it is reported that volumetric modulated arc treatment plan yields similar target coverage but lower monitor unit (MU) and treatment time for GBM radiotherapy in comparison to IMRT plan [8-11].

For an open treatment field, the homogeneous dose distribution can be obtained by flattening the radiation beam emerging from medical linear accelerators. Flattening of the radiation beam is achieved by placing flattening filter (FF) into the path of photon beam. In recent decades, there has been an increasing trend of using the flattening filter-free (FFF) radiation beam in radiotherapy treatment that is produced by the removal of FF from linear accelerator head. With the recent progress in linear accelerator technology, the clinical uses of FFF photon beams in radiotherapy treatments have progressively become the limelight [12].

The FFF radiation beams are characterized by high-dose rate, conical-beam profile, softened beam quality, shorter beam-on time (BOT), higher superficial dose, and lower out-of-field dose [13]. However, several researchers have investigated the dosimetric comparison of FFF photon beams with FF photon beams and concluded that FFF beams give similar dose distribution as FF beams [14, 15].

Reiber J et al. compared the treatment plan quality of brain metastases with radiosurgery using three-dimensional conventional technique and FFF photon beams [16]. In the aforementioned study, it was revealed that FFF photon beam provides desired dose distribution as FF photon beams but with lower dose spillage to normal brain. Therefore, it is required to investigate whether there are advantages in radiotherapy treatment of GBM using FFF photon beams, compared to that of FF photon beams with IMRT technique. The present study aimed to determine the dosimetric differences between 6MV FF and 6MV FFF photon beams in the treatment of GBM with IMRT technique and detect the most appropriate radiotherapy treatment modality.

## Materials and Methods

A total of 10 patients were randomly selected from our in statute database (Department of Radiotherapy, Chirayu Medical College and Hospital, Bhopal-462030 (M.P.), India

All the selected subjects were diagnosed with GBM and underwent IMRT treatment technique on Vital Beam linear accelerator (M/S Varian Medical Systems,

Palo Alto, CA, USA). Vital beam linear accelerator consists of 6MV, 10MV, as well as 15MV flattened and 6MV flattening filter-free photon beams. It is also equipped with five electron beams of energy, including 6MeV, 9MeV, 12MeV, 18MeV, and 20MeV. The analytical anisotropic algorithm (AAA) with 0.25 cm grid size was used for photon dose calculation for both types of plans.

The patients were treated in supine position keeping head towards gantry with a personalized thermoplastic mask. Computed tomography (CT) images of 0.2 cm slice thickness were utilized for treatment planning using the Eclipse treatment planning system (TPS) (version 13.6.23, Varian Medical Systems, Palo Alto, CA, USA). The CT images of each patient were then co-registered with respective brain magnetic resonance images (MRIs). This image fusion will help to delineate the target area and surrounding healthy tissues. T1-weighted MRI images with gadolinium contrast were used to delineate the gross tumor volume (GTV). The clinical target volume (CTV) was obtained by giving a symmetrical margin of 2-2.5 cm around the GTV. Again this volume was modified to include the areas of fluid-attenuated inversion recovery abnormalities and tumor infiltration to respective normal anatomic barriers.

Further expansion of the CTV margin by 0.5-0.7 cm leads to planning target volume (PTV). The target volumes (i.e., GTV, CTV, and PTV) were contoured in accordance with the guidelines of the European Society for Radiotherapy and Oncology and Advisory Committee on Radiation Oncology Practice [17]. The optic chiasm, optic nerves, brainstem, eye lens, pituitary gland, brain, and cochleae were contoured on the CT simulator images assisted by the fused T2-weighted MRI images. The PTV was excluded during the brain contouring as an organ at risk.

## Dose Prescription and Optimization Objective

The IMRT technique was used to irradiate the PTV to a dose of 60Gy in 30 fractions. Planning objective was to achieve 95% prescription dose (PD) to 95% of PTV with not more than 2% of PTV volume receiving 107% of PD as recommended by International Commission of Radiation Units and Measurements (ICRU) Report 83 [18]. All the IMRT treatment plans were optimized in such a way that the dose constraints for organs at risk (OARs) were kept as follows:

For each eye lens maximum point dose ( $D_{max}$ )  $\leq 7$  Gy, for each cochlea  $D_{max} \leq 45$  Gy and mean dose ( $D_{mean}$ )  $\leq 30$  Gy, for each eye  $D_{max} \leq 50$  Gy,  $D_{max}$  dose for the optic chiasm and optic nerves  $\leq 54$  Gy, for the brain stem  $D_{max} \leq 55$  Gy, and for planning risk volume brainstem  $V_{59Gy} \leq 0.01$  cc

## Radiotherapy Plans

Treatment Planning was performed using two photon beams, including 6MV FF (6MV\_FF) and 6MV FFF (6MV\_FFF) of Varian Vital Beam linear accelerator installed with millennium 120 MLC (Multileaf collimator). The MLC consists of 60 leaf

pairs with the width of inner 20 leaf pairs and outer 20 leaf pairs at isocenter as 0.5 and 1 cm, respectively. Linear accelerator was calibrated to produce 1 cGy per MU at  $D_{max}$  on the central axis for an open field of 10×10 cm at source to surface distance of 100 cm for both 6MV\_FF and 6MV\_FFF photon beams.

Plans were optimized by selecting maximum dose rates of 600MU/min and 1,400MU/min for 6MV\_FF and 6MV\_FFF photon beams, respectively. For all the selected patients, two IMRT plans of 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT were generated using TPS. Hypothetically additional IMRT plan with 6MV\_FFF beam was created by direct changing of photon beam of the original plan of 6MV\_FF to 6MV\_FFF without changing the original plan optimization parameters.

Inverse optimization was performed using original plan parameters followed by photon dose calculation using the AAA with 0.25 cm grid size. Eclipse TPS (version 13.6.23) includes dose volume optimizer (DVO) and photon optimizer (PO) for IMRT optimization. The DVO algorithm is used in Eclipse IMRT to generate optimal field shape and intensity [19]. Simple gradient optimization technique was used in a dose optimization algorithm that performs the optimization by minimization of the problem. The fluences are modified after each and every iteration performed by a dose optimization algorithm, and after each modification doses were calculated from the fluences.

As doses are calculated, the objectives at the points and derivatives of the point objectives are evaluated at the points of clouds constituting the patient volumes. The cost functions and their derivatives are calculated at each point in each structure. The derivatives of the cost function are back-projected to the fluences resulting in gradient. The DVO algorithm calculates the difference between the intermediate dose and first-round optimization result. It uses this difference to compensate for the optimal finding in the consequent iterations. On the other hand, PO algorithm optimizes static field IMRT and rapidArc plan.

The primary difference between PO algorithm and DVO optimization algorithm is that in DVO algorithm point cloud model was used to define the structures. On the other hand, a new structural model was used in PO algorithm to define structures, dose-volume histogram (DVH) calculation, and dose sampling. In PO algorithm, structures were spatially defined using one single matrix over the entire image. Voxel resolution of the matrix is defined using fixed values of 1.25, 2.5, or 5 mm, and this resolution is used to determine the planar X and Y resolution in the slices.

The Z resolution is perpendicular to the slice that is the function of the chosen resolution and slice thickness. The above-defined matrix identifies the structures and dose sampling and replaces the formerly used point clouds. Weighted volume of each voxel is utilized for the calculation of DVH for the structures. In the present study, PO was chosen over DVO for inverse optimization of all the IMRT plans because PO

generates better plan quality in a shorter period of time, compared to DVO [20].

Combinations of 5 to 7 noncoplanar and planar beams were chosen for IMRT planning. Noncoplanar beam arrangements are helpful in order to achieve better conformity of target and sparing of normal adjacent tissues and enable fast dose fall-off outside the target. In this study, whenever required a noncoplanar beam arrangement was used by tilting a patient couch to either 90° or 270° depending upon PTV extent and location.

Beam angles were chosen in order to cover the entire PTV and exclude any nearby normal organs. In addition, the collimator rotation of 3-5° was used in each beam angle to reduce tongue and groove effect of MLC, which decreases the inter-leaf leakage. All IMRT treatment plans were created by a sole medical physicist in order to avoid different planning strategies.

#### **Plan Evaluation and Statistical Methods:**

As per ICRU Report 83[18], doses to the PTV and OARs were recorded from their corresponding cumulative dose-volume histograms (c-DVHs).

#### **Homogeneity Index**

Homogeneity index (HI) was evaluated as the difference between the delivered dose to 2% ( $D_{2\%}$ ) and 98% ( $D_{98\%}$ ) of PTV volume divided by dose to 50% of PTV volume ( $D_{50\%}$ ) that is defined as follows:

$$HI = (D_{2\%} - D_{98\%}) / D_{50\%} \quad (1)$$

The HI value to zero indicates a completely homogeneous dose distribution.

#### **Conformity Index**

Conformity index (CI) is a ratio evaluating the coverage of the prescription dose in treatment plans defined as follows:

$$CI = VRI / TV \quad (2)$$

Where VRI (volume of reference isodose) is the volume encompassed by the 95% prescription isodose lines, and TV (target volume) is the PTV volume. In the present study, 95% isodose lines were chosen as reference isodose lines. In addition, unitary CI indicated desirable dose conformity. Moreover, treatment parameters, including the MU and BOT, for each treatment plan were recorded for evaluation. The BOT was defined as the radiation delivery time and did not incorporate gantry movement, patient positioning, and setup verification procedures.

#### **Statistical Tools**

A significance test was used to quantify the differences between the dosimetric planning parameters in 6MV\_FF\_IMRT and 6MMV\_FFF\_IMRT plans. Paired sample t-test was employed for scoring the significance level of observed differences between the obtained data using SPSS software (release 20.0, SPSS

Inc., Chicago, IL, USA). P-value less than 0.05 was considered statistically significant.

### Results

All the plans were optimized to achieve clinical and dosimetric goals of the present study. Patient-specific quality assurance of the treatment plan was performed for both types of planning strategies. Figure 1 illustrates the isodose distribution of IMRT plans generated with 6MV\_FF and 6MV\_FFF photon beams. The IMRT fluence verification was performed with OCTAVIUS 4D phantom. Both types of plans showed gamma passing rate higher than 95% while keeping planning evaluation criteria to 3%, 3mm.

Table 1 tabulates the patient characteristics. All the subjects selected in this study were diagnosed with GBM and previously treated by IMRT technique with 6MV\_FF photon beam. Out of 10 selected patients, 6 case were male and 4 case were female with the mean ages of  $45.0 \pm 3.74$  and  $50.5 \pm 12.65$  years, respectively. In the patient dataset, one, one, and eight subjects were diagnosed with stages IIIB, IIIA, and IV, respectively, according to the guidelines of the National Comprehensive Cancer Network. All the selected patients were also subjected to receive concurrent chemotherapy. The PTV was within the range of 184.5-554.3cc with a mean volume of  $360.88 \pm 135.57$  cc.

### Target Coverage and Dosimetric Parameter Analysis

All the dosimetric parameters for both 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans were evaluated based on c-DVH as shown in Figure 2. The DVH parameters and treatment plan evaluation indices are listed in Table 2. The  $D_{95\%}$  of PTV coverage was slightly higher in 6MV\_FF\_IMRT plan than that in 6MV\_FFF\_IMRT plan ( $P < 0.05$ ). The mean dose to PTV was moderately higher in 6MV\_FF\_IMRT plan; however, it was not statistically significant, compared to that in 6MV\_FFF\_IMRT plan ( $P > 0.05$ ). Dosimetric parameters ( $D_{98\%}$ ,  $D_{min}$ , and  $D_{2\%}$ ) of PTV coverage were higher when using 6MV\_FF photon beam in IMRT plan than those while using 6MV\_FFF photon beam. For  $D_{98\%}$ ,  $D_{min}$ , and  $D_{2\%}$  of the PTV coverage, the differences were statistically insignificant between 6\_MV\_FF\_IMRT and 6\_MV\_FFF\_IMRT plans ( $P > 0.05$ ).

The CI values were 0.99 and 0.98 in 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively, indicating that 6MV\_FF photon beam generated highly conformal IMRT plans in comparison to 6MV\_FFF photon beam IMRT plan. The HI values of  $0.0471 \pm 0.019$  and  $0.051 \pm 0.022$  were obtained for 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively. Lower HI value in 6MV\_FF\_IMRT plan than that in 6MV\_FFF\_IMRT plan showed superior homogeneous dose distribution in 6MV\_FF\_IMRT plan.

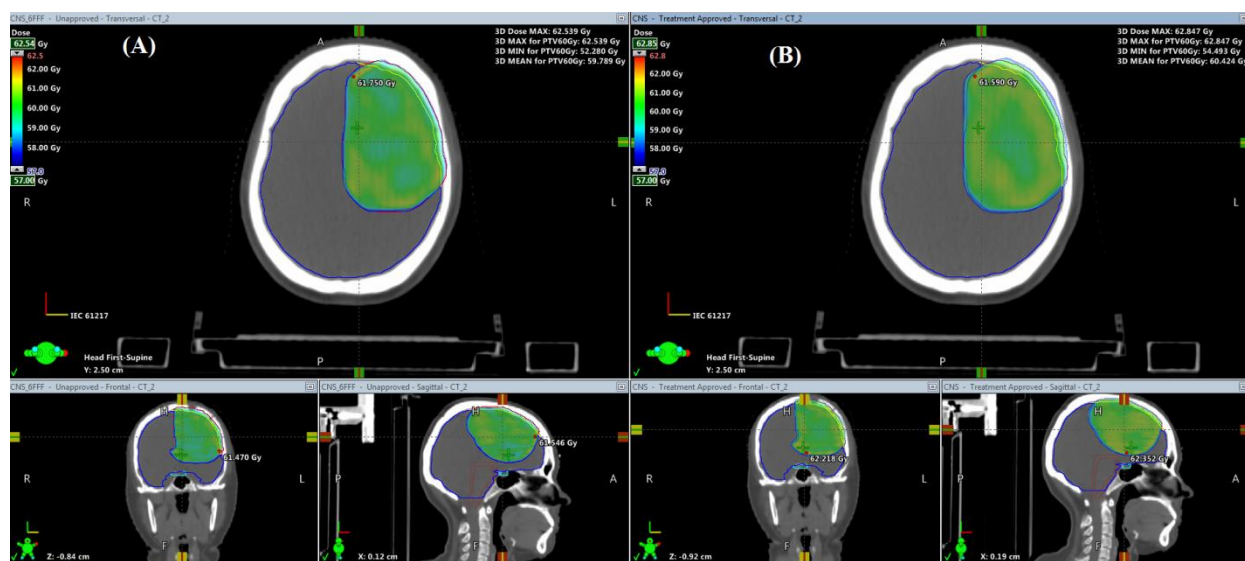


Figure 1. Intensity-Modulated radiation therapy (IMRT) isodose distribution generated from Eclipse treatment planning system in case of glioblastoma for same patient in axial, coronal, and sagittal planes with (A) 6MV flattened filter IMRT and (B) 6MV flattening filter-free IMRT

Table 1. Patient characteristics and staging

Patient	Gender	Age (years)	Tumor stage	PTV volume (cc)
1	M	43	IV	245.2
2	M	50	IV	227.9
3	M	46	IV	455.4
4	F	37	IIIA	302.4
5	M	46	IV	545.6
6	M	40	IV	184.5
7	F	52	IV	554.3
8	F	42	IV	464.6
9	M	46	IIIB	360.7
10	F	67	IV	268.2

PTV Volume (cc): 360.88±135.57(mean±S.D)  
 Range (cc): 184.52-554.3

Abbreviations: M: Male, F: Female, PTV: Planning target volume, cc: Cubic centimeter, S.D: Standard deviation

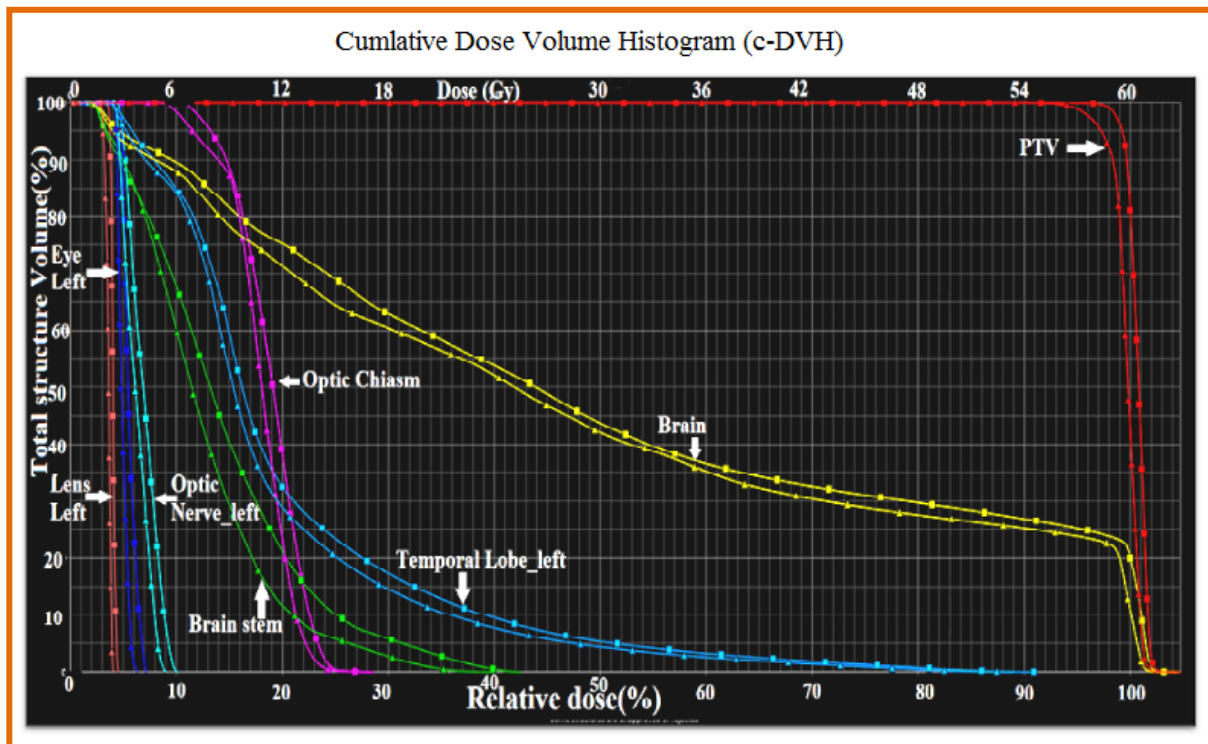


Figure 2. Comparison of the dose-volume histogram of planning target volume and organs at risk for 6MV flattened filter intensity-modulated radiation therapy (Square) and 6MV flattening filter-free intensity-modulated radiation therapy (Triangle) treatment plans

Table 2. Dosimetric comparison between 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans

Variables	6MV_FF_IMRT (mean±S.D)	6MV_FFF_IMRT (mean±S.D)	P-value
D <sub>95%</sub> (Gy)	58.87±0.74	58.20±0.69	<0.05
D <sub>2%</sub> (Gy)	60.88±0.82	60.40±0.64	>0.05
D <sub>98%</sub> (Gy)	58.06±1.16	57.38±1.21	>0.05
D <sub>max</sub> (Gy)	62.65±1.19	62.55±1.03	>0.05
D <sub>min</sub> (Gy)	50.20±3.25	49.82±3.46	>0.05
D <sub>mean</sub> (Gy)	59.84±0.58	59.39±0.55	>0.05
HI	0.047±0.019	0.051±0.22	>0.05
CI	0.99±0.01	0.98±0.01	>0.05

Abbreviations: HI: Homogeneity index, CI: Conformity index, D<sub>95%</sub>: Dose received by 95% of PTV volume, D<sub>2%</sub>: Dose received by 2% of PTV volume, D<sub>98%</sub>: Dose received by 98% of PTV volume, D<sub>max</sub>: Maximum dose, D<sub>min</sub>: Minimum dose, D<sub>mean</sub>: Mean dose, Gy: Gray, S.D: Standard deviation, PTV: Planning target volume, 6MV\_FF\_IMRT:6MV flattened filter intensity-modulated radiation therapy, 6MV\_FFF\_IMRT:6MV flattening filter-free intensity-modulated radiation therapy

Table 3. DVH parameters for organs at risk

OARs	Planning objective and OARs constraints	6MV_FF_IMRT (mean±S.D)	6MV_FFF_IMRT (mean±S.D)	P-value
Brainstem D <sub>max</sub> dose (Gy)	D <sub>max</sub> < 54 Gy	42.2±13.2	40.7±13.7	0.014
Pituitary mean dose (Gy)	Mean < 30 Gy	23.66±18.81	23.12±18.56	0.038
Eye dose (Gy) ipsilateral	D <sub>max</sub> < 50 Gy	28.27±10.93	25.84±10.76	0.02
Contralateral		20.83±13.13	19.33±12.51	0.018
Lens dose (Gy) ipsilateral	D <sub>max</sub> < 7 Gy	7.408±5.86	6.34±5.14	0.005
Contralateral		5.01±2.10	4.44±1.86	0.013
Optic nerve dose (Gy) ipsilateral	D <sub>max</sub> < 54 Gy	32.59±20.53	30.26±19.81	0.089
Contralateral		30.27±17.86	20.32±16.35	0.075
Optic chiasm dose (Gy)	D <sub>max</sub> < 55 Gy	36.93±17.43	34.95±17.22	0.077
Brain D <sub>mean</sub> dose (Gy)		33.5±7.02	32.8±6.88	0.017
V <sub>10Gy</sub> (cc)		594.8±145.7	581.43±140.76	0.031
V <sub>20Gy</sub> (cc)		413.9±86.93	399.2±83.87	0.031

Abbreviations: DVH: Dose-Volume histogram, OARs: Organs at risk, Gy: Gray, D<sub>mean</sub>: Mean dose, D<sub>max</sub>: Maximum dose, V<sub>10Gy</sub>: Volume receiving 10 Gy dose, V<sub>20Gy</sub>: Volume receiving 20 Gy dose, S.D: Standard deviation, cc: Cubic centimeter, 6MV\_FF\_IMRT:6MV flattened filter intensity-modulated radiation therapy, 6MV\_FFF\_IMRT:6MV flattening filter-free intensity-modulated radiation therapy

Table 4. Beam parameters calculated for one treatment fraction

Variables	6MV_FF_IMRT (mean±S.D)	6MV_FFF_IMRT (mean±S.D)	P-value
MU	627.68±122.72	889±254	0.0005
BOT (min)	1.05±0.2	0.64±0.18	0.000

Abbreviations: MU: Monitor unit, BOT: Beam-on time, S.D: Standard deviation, 6MV\_FF\_IMRT:6MV flattened filter intensity-modulated radiation therapy, 6MV\_FFF\_IMRT:6MV flattening filter-free intensity-modulated radiation therapy

**Dosimetric Analysis for Organs at Risk**

Table 3 shows the dosimetric parameter for the OARs. The D<sub>max</sub> dose to the brainstem reduced significantly from 42.2±13.2Gy in 6MV\_FF\_IMRT plan to 40.7±13.7 Gy in 6MV\_FFF\_IMRT plan (P=0.014). Pituitary gland mean dose was within tolerance limit in both types of IMRT planning, and there was a significantly lower mean dose in case of 6MV\_FFF\_IMRT plan than that in 6MV\_FF\_IMRT plan (P=0.038). The maximum dose to the ipsilateral eye in 6MV\_FF\_IMRT plan was 28.27±10.93Gy that reduced to 25.84±10.76Gy in 6MV\_FFF\_IMRT plan.

There was a significantly higher (8.6%) D<sub>max</sub> dose for the ipsilateral eye in 6MV\_FF\_IMRT plan than that in 6MV\_FFF\_IMRT plan. For the contralateral eye, D<sub>max</sub> doses were 20.83±13.13 and 19.33±12.51Gy in 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively. There was a significantly higher (7.2%) D<sub>max</sub> dose for the contralateral eye in 6MV\_FF\_IMRT plan than that in 6MV\_FFF\_IMRT plan.

For ipsilateral lens, D<sub>max</sub> doses were 7.408±5.86 and 6.34±5.14Gy in 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively. In 6MV\_FF\_IMRT plan, ipsilateral lens maximum dose was exceeding the tolerance dose of 7Gy. Contralateral lens D<sub>max</sub> dose was 5.01±2.10 Gy in 6MV\_FF\_IMRT plan that decreased to 4.44±1.86 Gy in 6MV\_FFF\_IMRT plan. For ipsilateral optic nerve, D<sub>max</sub> doses of 32.59±20.53 and 30.26±19.81Gy were obtained in 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively. In this regard, there was an insignificant difference between the plans (P=0.089).

Contralateral optic nerve D<sub>max</sub> doses were 30.27±17.86 and 20.32±16.35 Gy in 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively. Contralateral optic nerve D<sub>max</sub> dose was observed to be higher in 6MV\_FF\_IMRT plans, compared to that in 6MV\_FFF\_IMRT plan. Optic chiasm D<sub>max</sub> doses obtained in 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans were 36.93±17.43 and 34.95±17.22Gy, respectively.

Mean dose to the brain was significantly higher in 6MV\_FF\_IMRT plan, compared to that in 6MV\_FFF\_IMRT plan ( $33.5 \pm 7.02$  and  $32.8 \pm 6.88$  Gy, respectively).  $V_{10Gy}$  and  $V_{20Gy}$  volumetric dose parameters for the brain were noticed to be significantly higher in 6MV\_FF\_IMRT plan, compared to those in 6MV\_FFF\_IMRT plan ( $P=0.031$ ). For  $D_{max}$  dose to optic chiasm, optic nerves, and pituitary gland, the dosimetric differences were not significant; however, they were observed to be quite higher in 6MV\_FF\_IMRT plan, compared to those in 6MV\_FFF\_IMRT plan.

#### Beam-On Time and Monitor Unit

Table 4 shows the average MU and BOT for 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans. Total MUs per fraction were significantly on higher side by 41% for the 6MV\_FFF photon beam plan, compared to those in the 6MV\_FF photon beam plan.

Average delivered number of MUs were  $627.68 \pm 122.72$  and  $889 \pm 254$  for 6MV\_FF\_IMRT and 6MV\_FFF\_IMRT plans, respectively.

The 6MV\_FFF photon beam delivered planned MU with 2.3 times faster dose rate than 6MV\_FF photon beam, thereby leading to 39% decrease in BOT in 6MV\_FFF\_IMRT plan with a statistically significant difference ( $P < 0.05$ ).

## Discussion

A comparative analysis of IMRT treatment plan technique using 6MV\_FF and 6MV\_FFF photon beams for glioblastoma was investigated in the present study. The data presented in this report demonstrated the advantage of 6MV\_FFF photon beam over 6MV\_FF photon beam in terms of superior sparing of the brainstem, eye, lens, and optic nerve. In addition, the dose tolerance of optic chiasm can be achieved using 6MV\_FFF photon beam without sacrificing target dose coverage.

While creating IMRT plan using 6MV\_FF and 6MV\_FFF photon beams, all planning conditions were kept the same in order to avoid any bias in treatment planning strategy. The  $D_{95\%}$  of PTV coverage was higher in IMRT plan with 6MV\_FF photon beam that showed better target conformity than its counterpart. Dose HI was inferior in IMRT plan generated with 6MV\_FFF photon beam than that with 6MV\_FF photon beam. This result is in agreement with earlier published studies [14,15].

The small and limited dosimetric differences in target volume coverage and dose homogeneity are unlikely to be clinically significant. Results of the present study demonstrated that there was dosimetrically comparable IMRT treatment plan quality with 6MV\_FFF and 6MV\_FF photon beams that is in agreement with the findings of a study by Zwahlen DR et al. [21]. According to the literature, it is shown that FFF photon beam in prostate cancer or nasopharynx carcinoma improves the protection of the rectum, bladder, and other related OARs [22,23].

In the present study, the superiority of 6MV\_FFF photon beam in IMRT treatment planning of GBM was observed in terms of sparing the normal tissue and reduced scattered dose. This finding is in line with the results of a study by Niyazi M et al. [17]. There was 3.6% higher  $D_{max}$  dose to the brainstem in 6MV\_FF\_IMRT plan, compared to that in 6MV\_FFF\_IMRT plan. The average dose for the pituitary gland was well within its dose tolerance limit of 30 Gy in both plans. It was found to be approximately 23% lower than our planning objective criteria.

Approximately 9.4% reduction in  $D_{max}$  dose to the ipsilateral eye was observed in 6MV\_FFF\_IMRT plan. Ipsilateral eye lens dose objective criteria for  $D_{max}$  dose of 7 Gy was not met in 6MV\_FF\_IMRT plan; however, lower  $D_{max}$  dose was successfully achieved in 6MV\_FFF\_IMRT plan. Moderately lower  $D_{max}$  dose to the optic nerves was obtained in IMRT plan generated with 6MV\_FFF photon beam than that with 6MV\_FF photon beam.

Dosimetric parameters (i.e.,  $D_{mean}$ ,  $V_{10Gy}$ , and  $V_{20Gy}$ ) of the brain were significantly lower in 6MV\_FFF\_IMRT plan than those in 6MV\_FF\_IMRT plan in the present study. Brain volume receives a lower scattered dose in IMRT plan with 6MV\_FFF photon beam, compared to that in 6MV\_FF photon beam without compromising the dose to the target volume. In a study carried out by Hall EJ et al. [24], it was demonstrated that the dose to surrounding healthy tissues (which are distant from the PTV) appears predominantly from collimator transmission and scatter radiation of the linear accelerator head. These doses are subjected to the number of delivered MUs, and such kind of undesirable doses can enhance the risk of secondary tumors [24]. Minimization of radiation doses to normal tissues is of great importance to minimize both acute and late toxicity of treatment and smooth conduct of treatment course.

As reported in previous studies conducted by Wolfgang L et al. [25] and Zhuang MZ et al. [26], there was a reduction in treatment delivery time and increase in MUs with FFF photon beam. In the present study, the average planned MU was significantly higher in 6MV\_FFF\_IMRT plan, compared to that in 6MV\_FF\_IMRT plan. There was on an average 262 higher number of MUs were required by 6MV\_FFF photon beam than 6MV\_FF photon beam to give somewhat similar dose distribution and target coverage.

This may be due to the removal of the flattening filter that results in the softening of the beam.

Therefore, the dose delivered by softening photon beam to deeper tissue reduced that requires higher MU to reach the same depth than conventional flattened photon beam. Higher MU requirement in FFF photon beam to generate a comparable plan leads to longer treatment time that is compensated by available higher dose rates in FFF mode. Finally, it was observed that the FFF-based treatment plans are superior to FF-based plan only regarding the healthy tissue sparing issues. Normal tissue complication probability is mainly due to the

cone-shaped profile of FFF photon beam. On the other hand, if the treatment factors and tumor control probability issue would be of more concern, the FFF-based treatment plan would lead to more desirable clinical outcomes.

## Conclusion

Obtained results of the present study showed that the lower volumetric dose parameter of the brain in 6MV\_FFF photon beam gave lower volume irradiation in low-dose regions than that in 6MV\_FF photon beam. Moreover, reduced scattered dose provided further brain sparing by potentially reducing acute radiation-induced toxicity. This will result in improving the patients' quality of life with limited survival and lead to the smooth conduct of treatment.

It was also concluded that the IMRT treatment plan with 6MV\_FFF photon beam produced clinically acceptable plans, compared to that with 6MV\_FF photon beam in the treatment of GBM. The FFF photon beam produced an IMRT treatment plan with significant sparing of OARs without much compromise in treatment plan quality in comparison to FF photon beam. Lower treatment delivery time without forfeiting the quality of treatment plan provided numerous advantages, such as reduced possibility of unwanted patient movement during treatment, smooth clinical workflow, and better treatment experience for the patient.

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