Iranian Journal of Medical Physics

ijmp.mums.ac.ir

Impact of 6 MV & 10 MV Flattened and Flattening Filter Free Beams in Whole Brain Radiotherapy: A Treatment Planning Study

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ARTICLE INFO

Article type:
Original Paper

Article history:
Received: Mar 03, 2020
Accepted: Jun 05, 2020

Keywords:
Whole Brain Radiotherapy
Hippocampus
Scalp Sparing
Flattened Beam
Flattening Filter Free Beam

ABSTRACT

Introduction: To study the impact of 6 MV and 10 MV flattened beam (FB) and flattening filter free (FFF) beam in whole brain radiotherapy (WBRT) by using volumetric modulated arc therapy (VMAT).

Material and Methods: Twenty WBRTpatients were selected randomly. The dose prescription was 30 Gy, which was delivered in ten fractions. The planning target volume (PTV) and organs at risk (OARs) were contoured. Four VMAT plans, including 6 MV FB, 6 MV FFF, 10 MV FB, and 10 MV FFF beam plans, were generated.

Results: The 6MV FB and FFF beam plans were statistically significant ($p<0.05$) in terms of the dose received by 98% of the PTV ($D_{98\%}$) (26.86 Gy vs. 27.31 Gy, P=0.006), the dose received by 95% of the PTV ($D_{95\%}$) (28.28 Gy vs. 28.52 Gy, P=0.038), 107% isodose (V107%) of the PTV (2.43% vs. 3.74%, P=0.001), $D_{100\%}$ of the hippocampus (9.31 Gy vs. 9.16 Gy, P=0.009), and the D_{mean} scalp (16.7 Gy vs. 16.8 Gy, p=0.035). The 10 MV FB and FFF beam plans showed significant differences in the conformity index (0.9 vs. 0.85, P=0.01), V107% of the PTV (1.68% vs. 4.54%, P=0.001), $D_{100\%}$ (10.08 Gy vs. 9.81 Gy, P=0.036), and D_{mean} of the hippocampus (12.78 Gy vs. 12.57 Gy, P=0.018). The 6 MV and 10 MV FFF beams showed homogeneous conformal plans, which required 18-19% more MUs, compared to the FB plans.

Conclusion: The 6 MV and 10 MV FB and FFFB spared the hippocampus and the scalp with acceptable target coverage in WBRT cases.

► *Please cite this article as:*
Suresh T, Madeswaran S.Impact of 6 MV And 10 MV Flattened And Flattening Filter Free Beams in Whole Brain Radiotherapy: A Treatment Planning Study. Iran J Med Phys 2021; 18: 218-225.10.22038/ijmp.2020.46947.1740.

Introduction

Brain metastasis is the most common tumor in 10-30% of cancer patients [1]. The best treatment modality for brain metastasis is whole brain radiotherapy (WBRT) to relieve the intracranial pressure and improve local tumor control. The most common side effects of WBRT include irreversible neurological sequelae, such as dementia, cerebellar dysfunction, and neurocognitive function decline (NCFD). To avoid NCFD, hippocampal sparing is generally recommended. The main function of the hippocampus is the formation of new memories, consolidation and retrieval of information, and cooperation in learning [2]. However, cranial radiation can damage the hippocampus in WBRT. Besides, radiation-induced damage to the hippocampus can affect learning and memory formation [3].

The Radiation Therapy Oncology Group (RTOG) 0933 trial [4] reported that preservation of memory function can be achieved by sparing the hippocampus, as reported in 113 WBRT patients. Previously, two bilateral open fields were used to treat patients with brain metastasis. However, hair loss was common in conventional treatments for these patients, since a 5-7 mm margin around the brain was countered, including the hair follicles. Overall, sparing of the hippocampus using three-dimensional conformal radiation therapy (3D-CRT) is difficult, because the hippocampus is surrounded by the planning target volume (PTV), and therefore, more time is required to generate a clinically acceptable plan. To avoid the mentioned problems, an intensity-modulated technique is needed, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT).

In the present study, the VMAT modality [5] was used to generate a highly conformal and homogenous plan by varying the dose rate, gantry, and multi-leaf collimator (MLC) speed. It should be noted that the VMAT plan requires fewer monitor units (MUs) and a shorter treatment duration as compared to fixed-field IMRT. Recently, the Varian TrueBeam accelerator has been designed, delivering flattened beams (FB) and flattening filter free (FFF) beams. The results of an experimental study and a Monte Carlo (MC)

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simulation [6, 7] showed that removal of the flattening filter in the path of the beam had some advantages, such as reduction of head scatter, lower out-of-field dose, reduced neutron production at higher energies (>15 MV), and increased dose rate as compared to FBs.

Most dosimetric studies of FFF beams have focused on breast [8, 9], lung [10], and cervicalcancer patients [11]. Besides, the dosimetric study of FFF beams in WBRT with hippocampus sparing is limited. The present study aimed to compare treatment planning parameters, such as target coverage, OAR dose, MU, conformity index (CI), homogeneity index (HI), and low-dose volume coverage in normal tissues, using 6 MV and 10 MV FB and FFF beams by the VMAT technique.

Materials and Methods

Patient selection, imaging, contouring, dose prescription, and optimization objectives for inverse treatment planning

Twenty WBRT patients were randomly selected in this study. The patients were assigned to a headrest, and Orfit immobilization was performed for reproducibility. The CT slices were taken within 3-mm intervals, and images were transferred to an Eclipse treatment planning system (TPS) for planning. The planning target volume (PTV) and OARs (i.e., lens, eyes, optic nerves, optic chiasm, hippocampus, and scalp) were delineated in the respective slices on the planning CT scan. The RTOG 0933 protocol was used for contouring and dose prescription. According to the RTOG 0933 protocol, the PTV was defined as the whole brain parenchyma, excluding the hippocampal avoidance region.

The hippocampal avoidance region was defined as a 5-mm uniform margin around the hippocampus. The total dose prescription was 30 Gy, delivered in ten fractions. According to the RTOG 0933 protocol, 90% of the PTV must be covered by a prescription dose of 30 Gy, with 2% of the PTV (D2%) receiving no more than 37.5 Gy and at least 98% receiving 25 Gy (D98%). The optic nerve and optic chiasm dose was 37.5 Gy at any point. Also, 100% of the hippocampus volume (D100%) must receive ≤10 Gy, with a maximum dose of ≤17 Gy. The dose for the scalp must be as low as reasonably achievable.

Planning technique

Treatment planning for all 20 patients was performed in the Eclipse TPS (v. 11.0). The VMAT planning was performed using 6 MV and 10 MV FB and FFF beams. The dose rate was set at 600 MU/min for 6 MV FB and 10 MV FB beams. In 6 MV FFF and 10 MV FFF beam plans, the dose rates were 1400 MU/min and 2400 MU/Min, respectively. The VMAT plans were generated with two full arcs of 360° in clockwise and counter-clockwise directions, with collimator rotations of 30° and 330°, one non-coplaner partial arc at a couch angle of 90°, and an arc angle of 130° in a clockwise direction.To minimize the dosimetric effect of the tongue-and-groove effect in the MLC, the collimator was rotated. The plans were delivered on a Varian TrueBeam linear accelerator with a high-definition (HD) MLC. Besides, dose calculations were performed using an anisotropic analytical algorithm (AAA) with a grid size of 2.5 mm.

Plan evaluations and statistical methods

All of the plans were analyzed based on the CI and HI. The HI for the PTV was calculated to evaluate the dose homogeneity in the target [12]:

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

where $D_{2\%}$, $D_{50\%}$, and $D_{98\%}$ denote the doses received by 2%, 50%, and 98% of the PTV, respectively; HI=0 represents a homogeneous dose distribution. Moreover, the CI was measured to evaluate the coverage of the prescription dose in the treatment plans:

CI= Volume within 98% isodose line / PTV

where CI=1 indicates a good dose conformity.

The IBM SPSS v. 20.0 (SPSS Inc., Chicago, IL, USA) was used to evaluate the differences between the FB and FFF beam VMAT plans. Statistical analyses were performed using paired sample t-tests. The level of statistical significance was set at $P<0.05$.

Results

All of the plans were evaluated based on the cumulative dose-volume histograms. The PTV coverage, CI, HI, dose delivered to OARs, treatment MU, and low dose volume coverage of normal tissues are presented in Table 1 (means, standard deviations, and significant paired t-test P-values). The isodose distribution and dose-volume histogram for one patient are also shown in Figure 1 to Figure 4.

All of the plans achieved PTV coverage and spared the hippocampus and the scalp, according to the RTOG 0933 criteria. The PTV coverage in the D98% region was 27.3 Gy for the 6 MV FFF plan and 26.86 Gy for the 6 MV FB plan (P=0.006). As for the 10 MV plans, the PTV coverage in D98% was 26.5 Gy in both FB and FFF beams, and no significant difference was found (P=0.908). However, a significant difference was found between the 10 MV FB and FFF plans in the D90% region of the PTV (P=0.023). On the other hand, in all 6 MV and 10 MV plans, the D90% coverage was 0.5% less. In the PTV, for 6 MV and 10 MV FB and FFF plans, the dose coverage was within 32.4 Gy in the D2% region ($P<0.05$). Also, the 107% isodose coverage (V107%) of the PTV was higher in 6 MV and 10 MV FFF beam plans as compared to the FB plans (3.7% for 6 MV FFF plan vs. 4.5% for 10 MV FFF plan), and the difference was significant (P=0.001).

Table 1. The target, OARs, body-PTV, and MU comparisons between the flattened beams (FB) and flattening filter free (FFF) beams for 6 MV and 10 MV energies (SD: Standard deviation)

Target and OARs	Parameters	Plans (mean±SD)				P-value	
		6 MV FB	6 MV FFF	10 MV FB	10 MV FFF	6 MV FB vs. 6 MV FFF	10 MV FB vs. 10 MV FFF
PTV30 Gy	$D_{98\%}$ (Gy)	26.86±1.35	27.31±1.04	26.52±1.57	26.5±1.50	0.006	0.908
	$D_{95\%}$ (Gy)	28.28±0.99	28.52±0.75	27.97±1.20	27.76±1.28	0.038	0.113
	$D_{90\%}$ (Gy)	29.21±0.66	29.32±0.51	28.97±0.89	28.7±1.02	0.177	0.023
	$D_{50\%}$ (Gy)	30.82±0.15	30.83±0.18	30.76±0.21	30.71±0.35	0.937	0.255
	D2% (Gy)	32.12±0.15	32.26±0.15	32.04±0.14	32.4±0.22	0.001	0.000
	HI	0.17±0.04	0.16±0.03	0.18±0.05	0.19±0.06	0.058	0.084
	CI	0.93±0.07	0.93±0.06	0.9±0.09	0.85±0.12	0.950	0.010
	V107(%)	2.43±1.21	3.74±1.63	1.68±0.96	4.54±1.81	0.001	0.001
Hippocampus	$D_{100\%}$	9.31±0.60	9.16±0.58	10.08±0.91	9.81±0.92	0.009	0.036
	D_{max}	16.45±1.24	16.52±1.24	17.13±1.24	17.02±1.13	0.354	0.182
	D_{mean}	11.95±0.77	11.85±0.90	12.78±0.92	12.57±0.90	0.176	0.018
Scalp	D_{mean}	16.7±3.44	16.8±3.45	16.21±3.15	16.2±3.18	0.035	0.736
Lens	D_{max}(Gy)	6.8±1.27	6.33±1.13	7.08±1.17	6.69±1.28	0.000	0.000
Eyes	D_{max}(Gy)	20.76±3.43	20.72±3.34	20.59±3.91	21.02±3.01	0.695	0.339
Optic nerves	D_{max}(Gy)	30.3±1.83	30.43±1.92	30±1.63	30.06±1.93	0.339	0.721
Brainstem	D_{max}(Gy)	32.77±0.47	33.16±0.70	32.66±0.46	33.13±0.66	0.007	0.001
Optic chiasm	D_{max}(Gy)	32.39±1.07	32.76±0.90	31.71±1.22	32.12±1.28	0.045	0.037
Cochlea	D_{mean}(Gy)	30.34±1.51	30.55±1.65	30.12±1.51	30.22±1.62	0.343	0.518
Body-PTV	D_{mean}(Gy)	10.62±2.07	10.54±2.04	10.49±2.03	10.24±2.05	0.045	0.001
Low-dose volume	1 Gy (%)	83.79±13.75	82.17±14.41	83.71±13.36	82.07±13.60	0.016	0.050
	2 Gy (%)	69.5±14.55	67.37±14.83	69.65±14.60	66.61±15.26	0.001	0.001
	3 Gy (%)	63.3±14.89	61.88±15.10	63.6±14.81	61.57±14.98	0.001	0.001
	4 Gy (%)	59.74±14.85	58.87±14.92	60.06±14.81	58.74±14.98	0.001	0.001
	5 Gy (%)	57.08±14.39	56.29±14.42	57.41±14.34	56.24±14.44	0.001	0.001
	10 Gy (%)	44.23±10.85	43.73±10.76	44.18±10.70	43.26±10.71	0.000	0.001
Monitor units (MUs)	MU	702.9±104.54	829.25±109.16	618.3±107.79	735.9±116.99	0.001	0.001

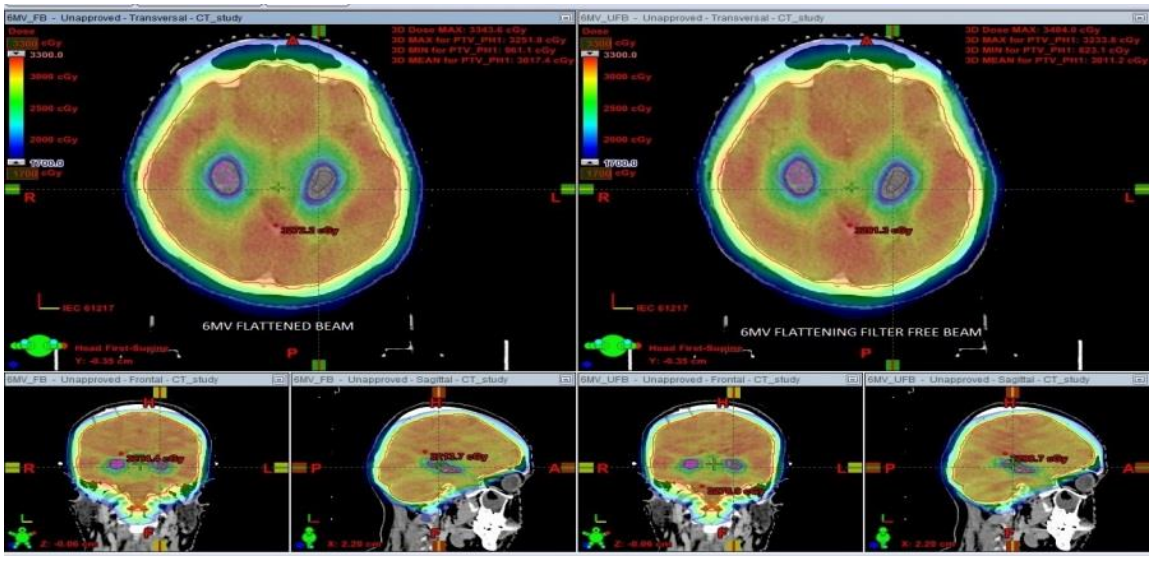

Figure 1. The isodose distribution generated by the VMAT planning for one patient in the axial, coronal, and sagittal planes with (a) 6 MV FB (left) and (b) 6 MV FFF (right) beam plans.

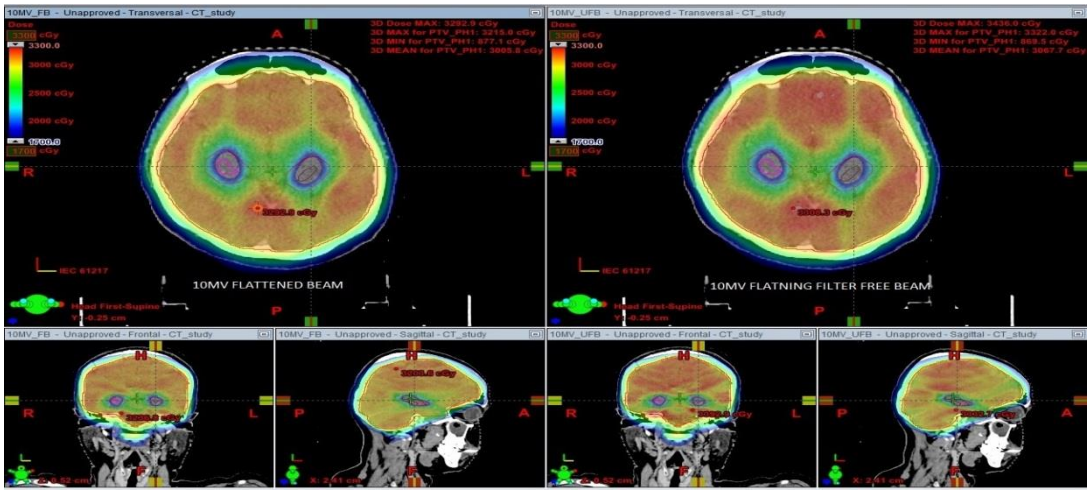

Figure 2. The isodose distribution generated by VMAT planning for one patient in the axial, coronal, and sagittal planes with (a) 10 MV FB (left) and (b) 10 MV FFF (right) beam plans

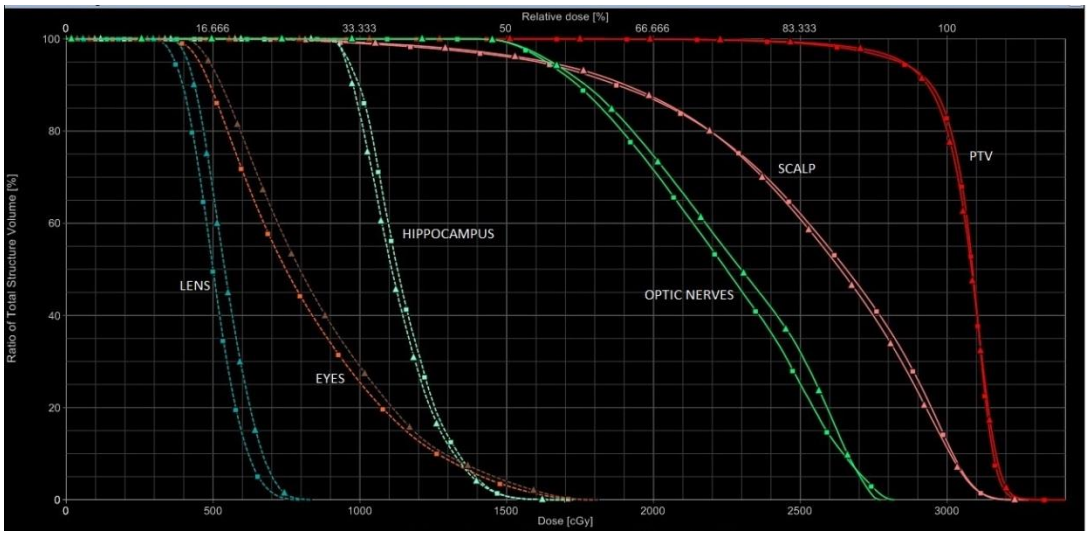

Figure 3. Comparison of the cumulative dose-volume histogram (cDVH) of 6 MV FB (square) and 6 MV FFF (triangle) beam plans of the PTV and OARs (lens, eyes, optic nerves, scalp, and hippocampus)

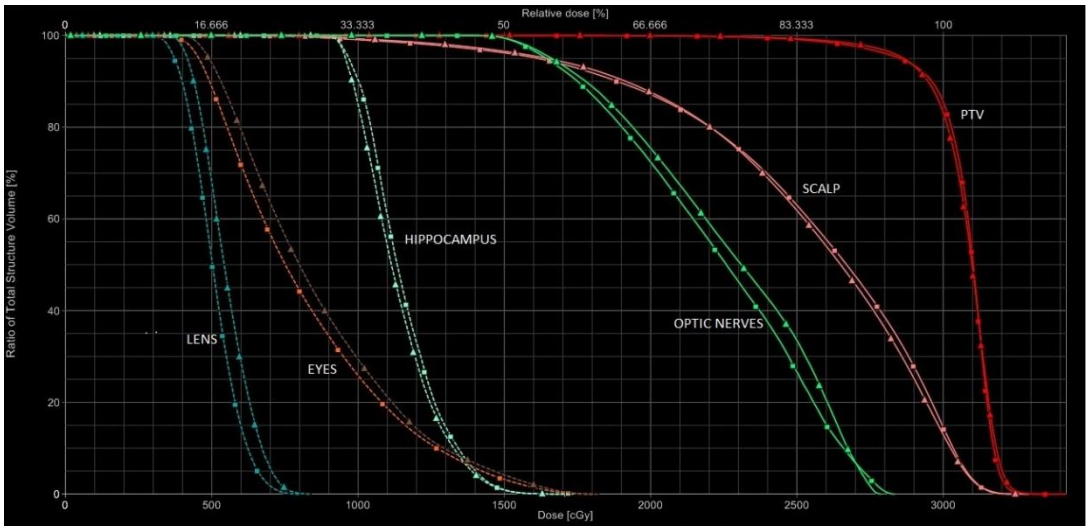

Figure 4.Comparison of the cumulative dose-volume histogram (cDVH) of 10 MV FB (square) and 10 MV FFF (triangle) beam plans of the PTV and OARs (lens, eyes, optic nerves, scalp, and hippocampus)

The HI (mean±SD) was superior in the 6 MV FFF plan (0.16±0.03) as compared to the 6 MV FB plan (0.17±0.04) (P=0.058). In the 10 MV plans, the HI value of FBs (mean±SD) was superior (0.18±0.05) to that of FFF beams (0.19±0.06); however, there was no significant difference (P=0.084). On the other hand, the CI was similar in 6 MV FB (0.93±0.07) and 6 MV FFF (0.93±0.06) plans (P=0.95). As for the 10 MV plans, the CI was superior in the FB plans (0.9±0.09) as compared to the FFF plans (0.85±0.12) (P=0.01).

The 6 MV FFF plan spared the $D_{100\%}$ regionof the hippocampus (9.16±0.58 Gy, P=0.009) significantly better than the 6 MV FB plan (9.31±0.60 Gy). Also, among 10 MV plans, the FFF beams spared the D100% region of the hippocampus (9.81±0.92 Gy) significantly better than the 10 MV FB plan (10.08±0.91 Gy) (P=0.036). The D_{max} of the hippocampus in 6 MV and 10 MV FFF plans was within 16.4 to 17.1 Gy, and the P-value was not significant. While no significant difference was found in the D_{mean} of the hippocampus for 6 MV FB and FFF beam plans, the difference was significant (P=0.018) for 10 MV FB (12.78±0.92 Gy) and 10 MV FFF (12.57±0.90 Gy) plans. The scalp D_{mean} was found to be lower in the 10 MV FB and FFF beam plans (16.2 Gy, P=0.736), although the difference was not significant. Conversely, the difference was significant between the 6 MV FB (16.7 Gy) and 6 MV FFF (16.8 Gy) plans regarding the scalp D_{mean} (P=0.035).

The lens D_{max} was 6.33 Gy in the 6 MV FFF plan as compared to 6.8 Gy in the 6 MV FB plan (P<0.05). The lens D_{max} was 7.08 Gy in the 10 MV FB plan and 6.69 Gy in the 10 MV FFF beam plan (P<0.05). The D_{max} of the eyes and optic nerves in all plans was 20.76 and 30.4 Gy, respectively, and no significant difference was found. Moreover, the D_{mean} of the cochlea in all plans was 30.55 Gy, and no significant difference was found. Also, the D_{max} of the brainstem and optic chiasma was 33.16 Gy and 32.76 Gy, respectively in all plans, and a significant difference was found.

Moreover, the body-PTV mean dose was found to be lower in the 6 MV FFF (10.52 Gy) and 10 MV FFF (10.24 Gy) beam plans as compared to 6 MV (10.62 Gy) and 10 MV FB plans (10.49 Gy) (P<0.05). The effects of low radiation doses of 1 Gy, 2 Gy, 3 Gy, 4 Gy, 5 Gy, and 10 Gy in the non-tumor volume were found to be lower in 6 MV and 10 MV FFF beam plans as compared to the FB plans. The MU was found to be higher in the 6 MV FFF (829 MU) and 10 MV FFF (735 MU) beam plans as compared to 6 MV (702 MU) and 10 MV (618 MU) FB plans (P<0.05).

Discussion

The physical characteristics of FB and FFF beams differ in terms of head scatter, dose rate, and peripheral dose. The FFF spectrum was soft due to the absence of flattening filter. The FB and FFF electron energies were the same at the target level, and the observed difference was attributed to the difference in penetration caused by beam hardening. Also, the absence of flattening filter resulted in reduced head scatter, increased dose rate (1400 MU/min for 6 MV FFF beams and 2400 MU/min for 10 MV FFF beams), reduced out-of-field dose, and reduced neutron contamination (≥15 MV) [8].

Considering the non-uniform dose profile of the FFF beam, in our study, the 6 MV and 10 MV FFF beam plans required more MUs to generate a uniform dose in the target volume. The FFF beam to FB beam MU ratio was 1.18 for 6 MV plans and 1.19 for 10 MV plans, as the increased dose rate and higher MU in the FFF beam plans did not reduce the beam-on time (BOT). In the 6 MV and 10 MV FB and FFF beam plans, the average BOT was onlyfour minutes. However, in the current study, the increased MU in the FFF beam plan reduced the OAR dose, similar to the hippocampal D100% (9.31 vs. 9.16 Gy), hippocampal D_{mean} (11.95 vs. 11.85 Gy), lens D_{max} (6.8 vs. 6.33 Gy), eyes D_{max} (20.76 vs. 20.72 Gy), and body-PTV mean dose (10.62 vs. 10.54 Gy) in 6 MV FB plans compared to FFF beam plans. In 10 MV FFF plans, the OAR dose reduced similar to the hippocampus D100% (10.08 Gy vs. 9.81 Gy), D_{max} (17.13 Gy vs. 17.02 Gy), D_{mean} (12.78 Gy vs. 12.57 Gy), and lens D_{max} (7.08 Gy vs. 6.69 Gy).

Lechner W et al. [13] found that with an increase in the MUs with FFF beams due to the non-uniform beam profile, more modulation was needed to generate a uniform dose to the target. Moreover, Siglin J et al. [14] reported that an inclined head angle of 30° and a seven-field coplanar IMRT plan would influence the hippocampal sparing, as compared to the flat head position of WBRT. The hippocampal $D_{max}$was 14.7 Gy, the $D_{100\%}$ was 7.4 Gy, and the D_{mean} dose was 9.3 Gy in the 30° head angle. Also, in the flat head position, the hippocampal D_{max} was 22.9 Gy in the $D_{100\%}$ of 9.2 Gy, with a mean dose of 11.7 Gy. In our study, all patients were positioned in a standard manner, without any head angle rotations; our plans also met the RTOG criteria. The hippocampal $D_{100\%}$ and D_{max} were 9.16-10.08 Gy and 16.45-17.13 Gy, respectively in the present study. In this regard, Kyung Su Kim et al. [15] reported that a head angle of 11° in the VMAT plan reduced the hippocampal $D_{100\%}$ to 10.45 Gy (D_{max}=13.7 Gy and D_{mean}=12 Gy) as compared to the non-inclined head position (hippocampal $D_{100\%}$=12.07 Gy, D_{max}=15.7 Gy, and D_{mean}=13.9 Gy).

Whole brain irradiation induces memory function deterioration [16] after completion of treatment within 8-10 months at a rate of 30% to 60%. In the RTOG 0933 protocol, the deterioration probability is about 17.2% at six months. Also, radiotherapy plays an important role in brain cancer. In this regard, Olsen E et al. [17] reported that 2-3 weeks after completion of radiation therapy, temporary alopecia occurs commonly, and hair growth occurs 2-3 months after the completion of radiotherapy. The International Commission on Radiological Protection Publication (ICRP) report 85 [18] reported that a single fraction dose of 7 Gy induced permanent epilation. Also, the collected data from the

historical Hiroshima atomic bomb survivors revealed that epilation occurred at 0.75 Gy radiation doses.

Many researchers [19-21] have reported that whole brain external beam radiotherapy of 2 Gy can cause temporary alopecia. J. Krayenbuehl et al. [22] reported that dose homogeneity and reduction of unnecessary hot spots in the brain could be achieved by using a Pinnacle automated planning system for HS-WBRT cases. In their study, the VMAT technique was used, and the beam setup consisted of two coplanner full arcs and two non-coplanar partial arcs (couch at 300°, arc range: 181° to 10°; couch at 60°, arc range: 350° to 179°). The hippocampal $D_{max}$was 14.1 Gy, the $D_{100\%}$ was 8.1 Gy, and the D_{mean} dose was 7.3 Gy. Also, the $D_{98\%}$ of the PTV was 25.2 Gy, the PTV V_{30} was 92%, the PTV D2% was 33.5 Gy, the HI was 0.24, and the treatment MU was nearly 1481.

Wang Y et al. [23] reported that the surface dose increased linearly with the field size (both 6 MV and 10 MV), and the FFF beams had a higher surface dose due to the contribution of low-energy photons (field size of 2×2 cm^2 to 10×10 cm^2) as compared to the FB beams. Kao et al. [24] reported that the IMRT WBRT plan reduced the scalp dose from 26.2 Gy to 16.4 Gy, which helped reduce transient alopecia in a short time and reduce the permanent alopecia risk. Moreover, Sood et al. [25] found that the scalp and cochlea mean doses in the VMAT plan were lower than the non-coplanar WBRT plan. The scalp mean dose in the VMAT versus non-coplanarWBRT was 19.33 Gy versus 28.14 Gy; also, the mean cochlea dose was 26.88 Gy versus 30.14 Gy. In our study, in all of the plans, the beam setup consisted of two full arcs in the coplanar direction and one partial arc in the non-coplanar direction; the scalp and cochlea mean doses were 16.8 Gy and 30.55 Gy, respectively.

Ghia A et al. [26] reported that hippocampal sparing is safe due to the lower incidence of metastasis at the 5-mm margin of the hippocampus. The metastasis risk in the hippocampus is estimated to be low. In this regard, Gondi V et al. [27] reported 1133 metastases in 371 patients, 8.6% of whom had metastasis in the 5-mm region of the hippocampus. However, according to the RTOG 0933 protocol, 98% of the target volume should receive a dose of 25 Gy to avoid cold spots and prevent the risk of local relapse. In the current study, in all plans, the $D_{98\%}$ received a dose of more than 25 Gy; therefore, the risk of local relapse was low in both FB and FFF beam plans.

The AAPM report TG-158 [28] defined a non-target dose as a dose outside the PTV (body-PTV), which is irradiated unintentionally. The non-target dose is defined to be as low as 3 Gy or 5% of the prescription dose. Fogliata et al. [29] reported that the non-target mean dose was in the range of 3 to 8 Gy in current craniospinal irradiation (CSI) cases. In our study, the non-target mean dose (body-PTV) was 10.62 Gy in the 6 MV FB plan and 10.54 Gy in the 6 MV UF plan. In the 10 MV FB and UF plans, the non-target mean doses were 10.49 Gyand 10.24 Gy, respectively. Moreover, Diallo ID et al. [30] found that if a normal tissue received a dose of 2.5 Gy or less, the secondary cancer risk increased in pediatric patients after radiotherapy. The second cancer risk might occur at a distance of 5 cm to 1 m from the PTV. Hall et al. [31] reported that the second cancer risk increased with an increase in the volume of normal tissue exposed to a low dose of radiation. In our study, the FFF beam plans showed that doses of 1 Gy, 2 Gy, 3 Gy, 4 Gy, and 5 Gy in the non-tumor area were low in comparison with the FB plans.

Additionally, Kragl G et al. [32] reported that the FFF beams reduced the head leakage by 52% in the 6 MV FFF plan and by 65% in the 10 MV FFF beam plan. Similarly, the peripheral dose was reduced at a rate of 23% for the 6 MV FFF beam plan and at 31% for the 10 MV FFF beam SBRT plan (20 cm from the field edge). Moreover, Kry SF et al. [33] reported that the peripheral dose at a distance of around 30 cm from the field edge was related to leakage radiation and that neutron production contributed to the out-of-field dose in energies above 10 MV. To reduce the neutron contamination in high energy beams, FFF beam is recommended The neutron production at higher energies is due to high energy photon interact with high atomic number material such as flattening filter, primary collimator, multi-leaf collimator in the linear accelerator head [34]. Recently, Sohrabi et al. [35] found that the fast, thermal and epithermal photo-neutrons produced in Siemens ONCOR medical linear accelerators, the measured dose equivalent at the isocenter in a 10 x 10 cm^2 field per 100 cGy of 6 MV X-rays is 0.0014% and 0.21% for 18 MV. The production of photoneutrons by 6 MV X-rays was about 150 times less than 18 MV X-rays; however, this value was clinically insignificant.

Conclusion

This study showed that the FFF beam spared the hippocampus and the scalp with an acceptable target coverage, according to the RTOG 0933 protocol. The VMAT therapy with FFF beams may help us eliminate uncertainties related to treatment delivery and a second cancer risk. Overall, the FFF treatment is safe, although further clinical studies are required.

Acknowledgment

The authors thank the authorities in Rajiv Gandhi Cancer Institute and Research Centre, Sector 5, Rohini, New Delhi, India, for their continued support and encouragement to complete this study.

References

1. Khuntia D, Brown P, Li J, Mehta MP. Whole‐brain radiotherapy in the management of brain metastasis. J ClinOncol. 2006; 24:1295‐304.
2. Lautin A: Limbic Brain. New York: Kluwer Academic/Plenum; 2001.

3. Tofilon PJ, Fike JR: The radioresponse of the central nervous system: a dynamic process. Radiat Res. 2000, 153(4):357‑70.
4. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampus neural stem‑cell compartment during whole‑brain radiotherapy for brain metastases (RTOG 0933): A phase II multi‑institutional trial. J ClinOncol. 2014; 32:3810‑6.
5. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. The British journal of radiology. 2011 Nov;84(1007):967-96. DOI: 10.1259/bjr/22373346.
6. Fippel M, Haryanto F, Dohm O, Nüsslin F, Kriesen S. A virtual photon energy fluence model for Monte Carlo dose calculation. Med Phys. 2003; 30:301 11.
7. Kry SF, Titt U, Pönisch F, Vassiliev ON, Salehpour M, Gillin M, et al. Reduced neutron production through use of a flattening filter free accelerator. Int J RadiatOncolBiol Phys. 2007; 68:1260 4.
8. Spruijt KH, Dahele M, Cuijpers JP, Jeulink M, Rietveld D, Slotman BJ, et al. Flattening filter free vs flattened beams for breast irradiation. Int J RadiatOncolBiol Phys. 2013; 85: 506‑13. DOI: 10.1016/j. ijrobp.2012.03.040 PMID: 22672750.
9. Tamilarasu S, Saminathan M, Sharma SK. Treatment Planning With Unflattened as Compared to Flattened Beams for Bilateral Carcinoma of the Breast. Asian Pacific journal of cancer prevention: APJCP. 2017;18(5):1377. DOI: 10.22034/APJCP.2017.18.5.1377.
10. Hrbacek J, Lang S, Graydon SN, Klock S, Riesterer O. Dosimetric comparison of flattened and flattening filterm free beams for stereotactic ablative radiotherapy of stage I non-small cell lung cancer. Med Phys. 2014; 41: 031709. DOI: 10.1118/1.4866231 PMID: 24593713.
11. Tamilarasu S, Saminathan M, Sharma SK, Pahuja A, Dewan A. Comparative Evaluation of a 6MV Flattened Beam and a Flattening Filter Free Beam for Carcinoma of Cervix‑IMRT Planning Study. Asian Pacific journal of cancer prevention: APJCP. 2018;19(3):639.
12. Vol I. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT): contents. J ICRU. 2010;10.
13. Lechner W, Kragl G, Georg D. Evaluation of treatment plan quality of IMRT and VMAT with and without flattening filter using Pareto optimal fronts. RadiotherOncol. 2013; 109: 437‑41. DOI: 10.1016/j.radonc.2013.09.020.
14. Siglin J, Champ CE, Vakhnenko Y, Witek ME, Peng C, Zaorsky NG, et al. Optimizing patient positioning for intensity modulated radiation therapy in hippocampal-sparing whole brain radiation therapy. Practical radiation oncology. 2014 Nov 1;4(6):378-83. DOI:10.1016/j.prro.2013.11.008.
15. Kim KS, Seo SJ, Lee J, Seok JY, Hong JW, Chung JB, et al. Inclined head position improves dose distribution during hippocampal-sparing whole brain radiotherapy using VMAT. Strahlentherapie und Onkologie. 2016 Jul;192(7):473-80. DOI: 10.1007/s00066-016-0973-0.
16. Gondi V, Hermann BP, Mehta MP, Tome WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J RadiatOncolBiol Phys. 2013; 85:348‑54.
17. Olsen E. Anagen hair loss: Radiation. In: Olsen EA, editor. Disorders of hair growth: Diagnosis and treatment. New York: McGraw Hill. 1994; 225‑6.
18. Valentin J. Avoidance of radiation injuries from medical interventional procedures. Ann ICRP. 2000; 30:7‑67.
19. Kyoizumi S, Suzuki T, Teraoka S, Seyama T. Radiation Sensitivity of Human Hair Follicles in SCID- hu Mice Radiation Research. 1998; 149:11‑8. DOI: 10.2307/3579676.
20. Potten CS, Burt PA, Roberts SA, Deshpande NA, Williams PC. Changes in the Cellularity of the Cortex of Human Hairs as an Indicator of Radiation Exposure Radiation and Environmental Biophysics Impact Factor. 1996; 35:121‑5. DOI: 10.1007/BF02434035.
21. Hamilton CS, Potten CS, Denham JW, O' Brien PC, Kron T. Response of Human Hair Cortical Cells to Fractionated Radiotherapy Radiotherapy and Oncology. 1997; 43:289‑92. DOI: 10.1016/S0167-8140(97)00059-5.
22. Krayenbuehl J, Di Martino M, Guckenberger M, Andratschke N. Improved plan quality with automated radiotherapy planning for whole brain with hippocampus sparing: A comparison to the RTOG 0933 trial. RadiatOncol. 2017; 12:161.
23. Wang Y, Khan MK, Ting JY, Easterling SB. Surface dose investigation of the flattening filter-free photon beams. International Journal of Radiation Oncology* Biology* Physics. 2012 Jun 1;83(2):e281-5.
24. Kao J, Darakchiev B, Conboy L, Ogurek S, Sharma N, Ren X, et al. Tumor directed, scalp sparing intensity modulated whole brain radiotherapy for brain metastases. Technology in cancer research & treatment. 2015 Oct;14(5):547-55.
25. Sood S, Pokhrel D, McClinton C, Lominska C, Badkul R, Jiang H, et al. Volumetric-modulated arc therapy (VMAT) for whole brain radiotherapy: not only for hippocampal sparing, but also for reduction of dose to organs at risk. Medical Dosimetry. 2017 Dec 1;42(4):375-83. DOI: 10.1016/j.meddos.2017.07.005.
26. Ghia A, Tomé WA, Thomas S, Cannon G, Khuntia D, Kuo JS, et al. Distribution of brain metastases in relation to the hippocampus: implications for neurocognitive functional preservation. International Journal of Radiation Oncology* Biology* Physics. 2007 Jul 15;68(4):971-7.
27. Gondi V, Tome WA, Marsh J, Struck A, Ghia A, Turian JV, et al. Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: Safety profile for RTOG 0933. RadiotherOncol. 2010; 95:327‑31.
28. Kry SF, Bednarz B, Howell RM, Dauer L, Followill D, Klein E, Paganetti H, et al. AAPM TG 158: measurement and calculation of doses outside the treated volume from external-beam radiation therapy. Medical physics. 2017 Oct 1;44(10):e391-429.
29. Fogliata A, Bergström S, Cafaro I, Clivio A, Cozzi L, et al. Cranio-spinal irradiation with volumetric modulated arc therapy: A multi-institutional

treatment experience. Radiotherapy and Oncol. 2011; 99: 79‑85.
30. Diallo I, Haddy N, Adjadj E, Samand A, Quiniou E, Chavaudra J, et al. Frequency distribution of second solid cancer locations in relation to the irradiated volume among 115 patients treated for childhood cancer. International Journal of Radiation Oncology* Biology* Physics. 2009 Jul 1;74(3):876-83.
31. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J RadiatOncolBiol Phys. 2003; 56 (1):83‑8.
32. Kragl G., Baier F., Lutz S. Flattening filter free beams in SBRT and IMRT: dosimetric assessment of peripheral doses. Z Med Phys. 2011;21(May (2)):91‑101.
33. Kry SF, Vassiliev ON, Mohan R. Out-of-field photon dose following removal of the flattening filter from a medical accelerator. Phys Med Biol. 2010;55(8):2155‑66.
34. Sohrabi M, Morgan KZ. Neutron dosimetry in high energy X-ray beams of medical accelerators. Phys Med Biol. 1979;24(4):756‑66.
35. Sohrabi M, Hakimi A. Novel 6MV X-ray photoneutron detection and dosimetry of medical accelerators. Phys Med. 2017; 36:103‑9.