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Dosimetric comparison of different radiotherapy techniques for the treatment of Retinoblastoma

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Original Article

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Abstract

Aim: This study aims to compare the dosimetric parameters among four different external beam radiotherapy techniques used for the treatment of retinoblastoma.
Materials and methods: Computed tomography (CT) sets of five retinoblastoma patients who required radiotherapy to one globe were included. Four different plans were generated for each patient using three dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and VMAT using flattening filter free (VMAT-FFF) beam techniques. Plans were compared for target coverage and organs at risk (OARs) sparing.
Results: The target coverage of planning target volume (PTV) for all the four modalities were clinically acceptable with a V95 of 95 ± 0%, 97·6 ± 1·87%, 99·3 ± 0·5% and 99·17 ± 0·45% for 3DCRT, IMRT, VMAT and VMAT-FFF respectively. The VMAT and IMRT plans had better target coverage than the 3DCRT plans ($p = 0{\cdot}001$ and $p = 0{\cdot}07$ respectively). IMRT and VMAT plans were also found superior to 3DCRT plans in terms of OAR sparing like brainstem, optic chiasm, brain ($p < 0{\cdot}05$). VMAT delivered significantly lower dose to the brainstem and contralateral optic nerve in comparison to IMRT. Use of VMAT-FFF beams did not show any benefit over VMAT in target coverage and OAR sparing.
Conclusion: VMAT should be preferred over 3DCRT and IMRT for treatment of retinoblastoma owing to better target coverage and less dose to most of the OARs. However, IMRT and VMAT should be used with caution because of the increased low dose volumes to the OARs like contralateral lens and eyeball.

Introduction

Retinoblastoma is the most common intraocular malignant tumour in childhood with reported cases of approximately 1 in 18,000 live births worldwide.[1,2] About 40% of the cases of retinoblastoma are hereditary due to germline mutations in the RB1 tumour-suppressor gene and 60% are sporadic.[3,4]

Management of retinoblastoma has notably changed over years as a result of the availability of different local treatments like cryotherapy, photocoagulation, plaque therapy and various newer chemotherapeutic agents.[5–9] Although a radiosensitive tumour, the role of external beam radiotherapy (EBRT) in the treatment of retinoblastoma has decreased over time. This is because of the increased risk of late toxicities caused by radiation especially second malignancies. As per the National Cancer Institute's Surveillance, Epidemiology and End Results database of the nine original tumour registries (SEER-9), the use of EBRT for retinoblastoma has decreased from 30% of treatments in the period from 1973 to 76 to 2% in the period from 2005 to 2008.[10–12]

Currently, EBRT is used in the treatment of retinoblastoma in situations of residual disease or recurrences after chemotherapy or local therapy, diffuse vitreous seeding and post enucleated retinoblastoma with sclera involvement, extraocular extension and optic nerve involvement.[10] Radiotherapy treatment delivery to the orbit is technically challenging due to presence of critical structures nearby. Traditionally anterior and lateral wedged portals were used to deliver the treatment. However, this results in dose heterogenicity within the target volume.

The modern radiotherapy delivery techniques such as intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and proton therapy achieve more conformal dose to the target volume and less doses to the surrounding normal structures.[13] However, IMRT increases the total integral dose by delivering a low dose to the surrounding structures, hence increasing the risk of second malignancies.[14] VMAT technique gives more dose homogenicity in the target volume while sparing normal structures than IMRT in various tumour sites.[15–17] In VMAT technique, there is a continuous change of multileaf collimator

(MLC) movement with gantry rotation and dose rate takes place with less monitor units (MU) and treatment delivery time.[17,18]

The study focussed on evaluation of four different EBRT techniques used for treatment of retinoblastoma when the target volume is the whole globe. Dosimetric comparison was carried out among the four EBRT techniques to find the optimum one.

Materials and Methods

Patient selection and simulation

This is a hospital-based dosimetric study conducted on the computed tomography (CT) sets of already treated patients. CT data sets of five children of post enucleated retinoblastoma who required radiotherapy to one globe were included in the study. The simulation was done in supine position using three clamped thermoplastic head mould. CT images were acquired in the Philips Brilliance big bore CT (Phillips Medical Systems Nederland B.V. Veenpluis, The Netherlands) machine according to standard procedures with 3-mm slice spacing.

Radiotherapy planning: techniques and objectives

The clinical target volume (CTV) was comprised of the eye globe and proximal 0·5 cm of the optic nerve. The planning target volume (PTV) was created by using uniform three dimensional 3-mm margin to the CTV. Four different plans for each patient were generated for comparison using three dimensional conformal radiotherapy (3DCRT) with two coplanar beams, IMRT with 7 dynamic delivery fields, single arc VMAT and VMAT using flattening filter free beams (VMAT-FFF). For uniform dosimetric comparison, dose prescription was 5,400 cGy in 30 fractions to the PTV for all the patients and plans.

The goal of treatment planning was to achieve clinically acceptable PTV coverage and organ at risk (OAR) sparing. 3DCRT plans were developed using two coplanar portals. Fields were shaped by using MLC blocking and an enhanced dynamic wedge was manually optimised to obtain uniform dose distributions in the PTV. The IMRT was planned with seven dynamic delivery fields. For the VMAT and VMAT-FFF plans, single full arc beams were used ranging from 181 to 179° in clockwise direction.

For all plans, the dose calculations and optimizations were performed using the Eclipse V 15.6 treatment planning system (Varian Medical Systems, Inc. Palo Alto, CA USA). The plans were generated by using 6-MV photons in Varian trilogy (Varian Medical Systems, Inc. Palo Alto, CA USA), equipped with Millennium 120 MLC. The central 20 cm leaf width projected at isocentre is 5 mm and outer 20 cm leaf width projected at isocentre is 10 mm with leaf transmission factor is 0.0145 for 6 MV photons.

A fixed dose rate of 600 MU/min was applied for 3DCRT and IMRT cases. Maximum dose rate for VMAT was 600 MU/min and for VMAT-FFF was 1,400 MU/min. Dose calculation was performed using the Anisotropic Analytical Algorithm (AAA) and grid spacing of 2·5 mm.

Planning objectives for PTV was, at least 95% of the PTV volume must be covered by 95% of the prescription dose and a maximum 107% of prescribed dose should be limited to less than 1% of volume. For the OARs the objectives were, the Brainstem D1% < 5,400 cGy, the Optic Chiasm D1% < 5,400 cGy, for contralateral lens D1% < 800 cGy, for contralateral eyeball Dmean < 4,000 cGy, for contralateral optic nerve D1% < 5,400 cGy.

Plan evaluation and comparison

Cumulative dose–volume histograms (DVH) calculated for each plan were used for quantitative evaluation of plans. For PTV, the values of D99 and D1% (dose received by the 99 and 1% of the volume respectively) were defined as metrics for minimum and maximum doses and consequently reported. V95 is the target volume expressed in percentage (%), which is covered by the 95% of the prescription dose.

Homogeneity Index (HI) is an objective tool to analyse the uniformity of dose distribution in the target volume. It was calculated by difference between D1 and D99% of PTV and divided by the prescription dose (Dp).[19,20]

$$\mathrm{HI} = (\mathrm{D1\%} - \mathrm{D99\%})/\mathrm{Dp}$$

Conformity index was calculated by using the formula as suggested by International Commission on Radiation Units and Measurements (ICRU) Report 62 that was originally reported in Radiation Therapy Oncology Group (RTOG) 90-05 protocol.[21,22]

$$\mathrm{CI} = \mathrm{TV}/\mathrm{V_{PTV}},$$

where TV is the volume for target enclosed by 95% of isodose lines, that is V95 and V_{PTV} is the geometric target volume calculated from DVH.

Statistical analysis

Results are described as mean ± standard deviation (SD). Comparison of different dosimetric parameters among the plans with different treatment techniques are analysed with *t*-test. Statistical analysis was conducted with Microsoft Office Excel 2007 and GraphPad Prism 8·3 1. Difference is considered statistically significant when $p < 0{\cdot}05$

Results

CT data sets of five patients were enrolled in the study and in total 20 plans were generated for these patients. Figures 1 and 2 depict typical dose distribution and DVH comparison among the four treatment techniques of one patient. Detailed dosimetric comparisons on target coverage are presented in Table 1. The target coverage of PTV for all the four modalities was clinically acceptable with a V95 of 95 ± 0%, 97·6 ± 1·87%, 99·3 ± 0·5% and 99·17 ± 0·45% for 3DCRT, IMRT, VMAT and VMAT-FFF respectively. VMAT technique showed statistically significant improved coverage of PTV in terms of V95 when compared with 3DCRT ($p = 0{\cdot}0001$). D1% (cGy), which is the matrix for maximum dose, was lowest for the PTV in IMRT technique (5483 ± 8·6) and highest for 3DCRT technique (5807·03 ± 149·3). Significant difference observed between 3DCRT versus IMRT ($p = 0{\cdot}02$) and IMRT versus VMAT ($p = 0{\cdot}001$), but not with VMAT versus VMAT-FFF ($p = 0{\cdot}2$). The HI of the 3DCRT, IMRT, VMAT and VMAT-FFF were 0·19 ± 0·08, 0·07 ± 0·01, 0·08 ± 0·005 and 0·09 ± 0·01 respectively.

Table 2 lists the OARs protection comparison among four planning modalities. For the contralateral optic nerve, lens and eyeball, the received doses were well below their respective tolerance limits.

The D1% (cGy) of the contralateral eyeballs were 670·2 ± 513·6, 1805·6 ± 56·2, 1864·1 ± 426·2 and 2170·8 ± 33·8 for 3DCRT, IMRT, VMAT and VMAT-FFF respectively. In this regard,

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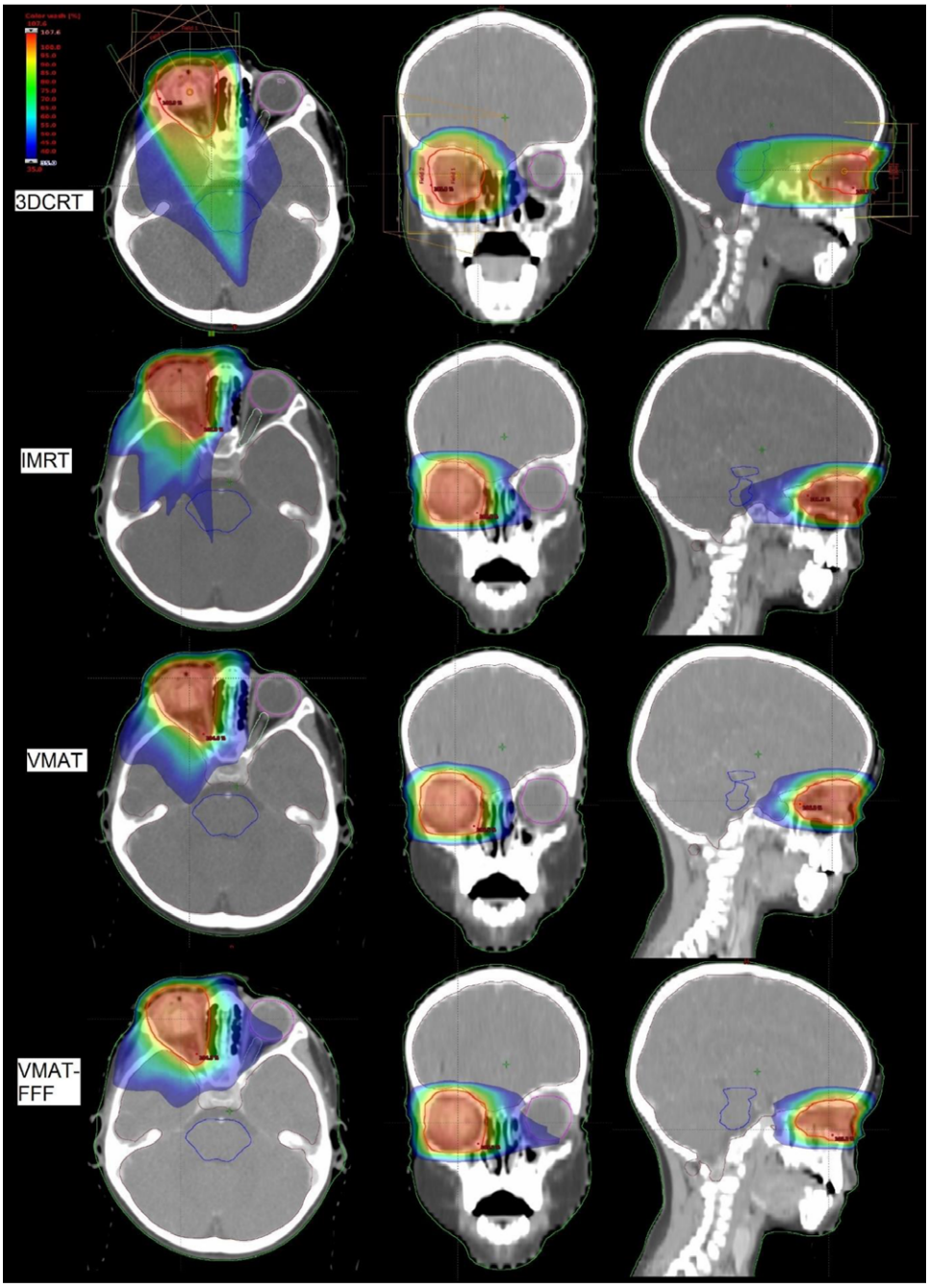

Figure 1. Dose distribution comparison among 3DCRT, IMRT, VMAT and VMAT-FFF for one patient.

3DCRT showed significant reduction of dose when compared with IMRT ($p = 0{\cdot}02$) and VMAT ($p = 0{\cdot}04$). But no differences were observed between IMRT versus VMAT ($p = 0{\cdot}8$) and VMAT versus VMAT-FFF ($p = 0{\cdot}2$).

The doses of optic chiasm for all the plans were within tolerance limit. The D1% (cGy) were $4622{\cdot}4 \pm 180{\cdot}9$, $2138{\cdot}1 \pm 322$, $2420{\cdot}1 \pm 169{\cdot}6$ and $2292{\cdot}1 \pm 188{\cdot}7$ for 3DCRT, IMRT, VMAT and VMAT-FFF respectively. Similarly doses to the brainstem for all the plans were within tolerance limit. The D1% of the brainstem was lowest for the VMAT-FFF technique ($1429{\cdot}37 \pm 279{\cdot}35$) and highest for the 3DCRT technique ($4189{\cdot}2 \pm 74{\cdot}58$). Significant difference was observed between 3DCRT versus IMRT ($p = 0{\cdot}0001$), 3DCRT versus VMAT ($p = 0{\cdot}0001$) and IMRT versus VMAT ($p = 0{\cdot}03$) but not with VMAT versus VMAT-FFF ($p = 0{\cdot}25$). The brain volumes receiving 500, 1,000 and 1,500 cGy were the greatest with the 3DCRT technique and maximum brain sparing achieved with VMAT technique. The average MUs of 3DCRT, IMRT, VMAT and VMAT-FFF plans were $210{\cdot}3 \pm 6{\cdot}8$, $617{\cdot}67 \pm 95{\cdot}4$, $456 \pm 15{\cdot}1$ and $452{\cdot}67 \pm 16{\cdot}2$ respectively. VMAT plans have a significantly lower MU delivery as compared to the IMRT plans ($p = 0{\cdot}04$); however, no significant difference was observed between VMAT and VMAT-FFF plans ($p = 0{\cdot}8$).

The IMRT and VMAT plans achieved better brain sparing than 3DCRT plans. The brain volumes receiving 500, 1,000 and 1,500 cGy (V500, V1000 and V1500) are shown in the Table 2. Statistically significant brain sparing of IMRT and VMAT plans were observed in terms of V10 and V15 when compared with 3DCRT plans ($p < 0{\cdot}05$).

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Table 1. Comparison of target coverage for different techniques

	3DCRT	IMRT	VMAT	VMAT-FFF	*P* Value			
PTV	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	3DCT versus IMRT	3DCRT versus VMAT	IMRT versus VMAT	VMAT versus VMAT-FFF
Dmean (cGy)	5555·13 ± 81·9	5342·77 ± 28·03	5464·17 ± 20·15	5462·77 ± 10·21	0·013	0·13	0·003	0·9
V95 (%)	95 ± 0	97·57 ± 1·88	99·3 ± 0·5	99·17 ± 0·45	0·07	0·0001	0·19	0·7
D1% (cGy)	5807·03 ± 149·27	5483 ± 8·62	5628·17 ± 11·26	5644·23 ± 14·34	0·02	0·1	0·0001	0·2
D99% (cGy)	4755·6 ± 301·56	5059·9 ± 87·94	5156·9 ± 41·46	5139·13 ± 36·26	0·16	0·08	0·15	0·6
HI	0·19 ± 0·07	0·07 ± 0·01	0·08 ± 0·005	0·09 ± 0·01	0·06	0·08	0·3	0·3
CI	0·95 ± 0·005	0·97 ± 0·01	0·97 ± 0·005	0·99 ± 0·006	0·09	0·001	0·189	1
MU	210·33 ± 6·8	617·67 ± 95·42	456 ± 15·09	452·67 ± 16·26	0·0018	0·0001	0·04	0·8

SD, standard deviation.

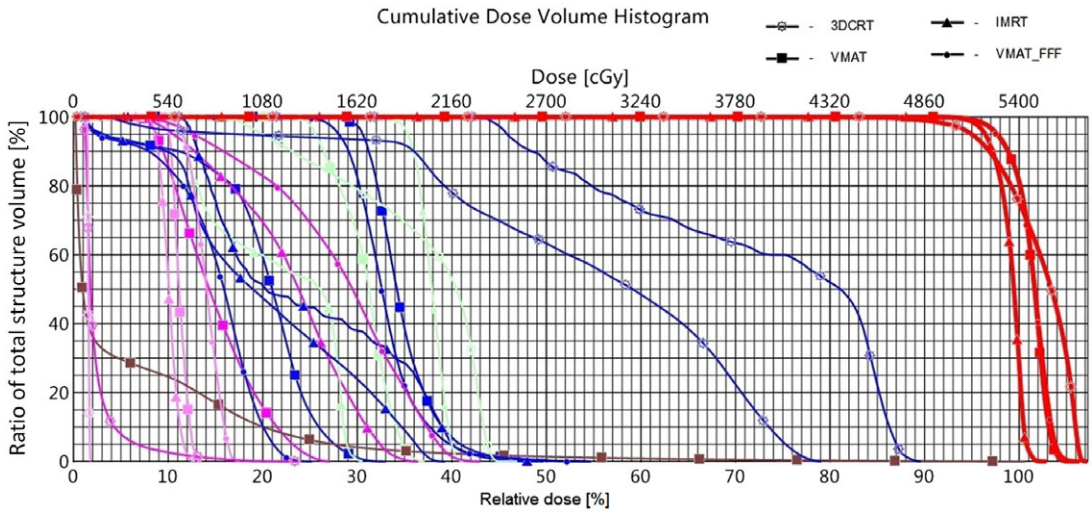

Figure 2. DVH comparison among 3DCRT, IMRT, VMAT and VMAT-FFF for one patient.

Discussion

Dosimetric parameters of four different EBRT techniques used for treatment of retinoblastoma were compared in this study. The 3DCRT plans resulted a higher HI indicating poor homogenicity. The IMRT and the VMAT plans were more homogeneous than the 3DCRT plans but the statistical difference only reached borderline significance (3DCRT versus IMRT, $p = 0{\cdot}06$ and 3DCRT versus VMAT, $p = 0{\cdot}08$). The VMAT and IMRT plans had better target coverage (V95) than the 3DCRT plans ($p = 0{\cdot}001$ and $p = 0{\cdot}07$ respectively). There was no significant difference on target coverage observed between IMRT versus VMAT and VMAT versus VMAT-FFF. 3DCRT plans showed highest value of maximum dose (D1) within the target volume.

Deng Z et al. evaluated the dosimetric advantages of VMAT in the treatment of primary and secondary intraocular cancer comparing directly with 3DCRT and IMRT. Although no clear distinction on PTV coverage among 3DCRT, IMRT and VMAT plans was observed in the treatment of intraocular cancer, VMAT and IMRT achieved better homogeneity and conformity for target volume.[20]

Due to the vicinity of critical organs, such as the lens, optic nerve, brainstem etc, optimising the dose coverage on target volumes while sparing critical organs has been a challenge in Radiotherapy of ocular malignancies. In this study, VMAT ($p = 0{\cdot}0001$) and IMRT ($p = 0{\cdot}0001$) plans significantly decreased the maximum dose (D1%) to the brainstem in comparison to the 3DCRT plans. In this regard, VMAT was found superior to IMRT plans ($p = 0{\cdot}03$) but there was no significant difference between VMAT and VMAT-FFF.

In this study, the IMRT and the VMAT plans showed a significant increase of Dose (D1%) to the controlateral lens and the eyeball as compared to 3DCRT plans. Similar results were obtained by Deng Z et al. where they have recorded increased dose to the controlateral eyeball and lens with IMRT and VMAT technique as compared to 3DCRT plans.[20] However, in our study, the dose to the contralateral optic nerve (D1%) is lower with IMRT and VMAT plans as compared to the 3DCRT plans.

As for the dose delivery to the optic chiasm (D1%), the IMRT and the VMAT plans delivered significantly lower dose when compared with the 3DCRT plans ($p = 0{\cdot}0003$ and $p = 0{\cdot}0001$

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Table 2. Comparison of OAR sparing for different techniques

OAR	3DCRT (Mean ± SD)	IMRT (Mean ± SD)	VMAT (Mean ± SD)	VMAT-FFF (Mean ± SD)	*P* Value 3DCT versus IMRT	*P* Value 3DCRT versus VMAT	*P* Value IMRT versus VMAT	*P* Value VMAT versus VMAT-FFF
D1% (cGy)	82·73 ± 20·38	715 ± 86·77	700·13 ± 28·2	812·17 ± 123·55	0·0003	0·0001	0·7	0·2
Dmean (cGy)	119·77 ± 57·58	1200·53 ± 92·6	1009·63 ± 200	1281·9 ± 253·8	0·0001	0·0018	0·208	0·2
D1% (cGy)	670·2 ± 513·61	1805·6 ± 56·2	1864·13 ± 426·2	2170·8 ± 33·8	0·019	0·0363	0·8	0·2
Brainstem								
D1% (cGy)	4189·2 ± 74·58	2131·5 ± 71·67	1703·77 ± 218·9	1429·3 ± 279·4	0·0001	0·0001	0·0324	0·2
D1% (cGy)	2205·4 ± 117·67	1722·7 ± 108·29	2066·8 ± 109·3	2191·2 ± 99·5	0·0159	0·3138	0·01	0·2
Optic Chiasm								
D1% (cGy)	4622·4 ± 180·94	2138·13 ± 321·96	2420·13 ± 169·6	2292·1 ± 188·7	0·0003	0·0001	0·2506	0·4
Brain								
V500 cGy (%)	25·8 ± 3·27	18·43 ± 3·81	21·27 ± 3·91	19·3 ± 2·55	0·06	0·19	0·4	0·5
V1000 cGy (%)	22·77 ± 3·14	10·03 ± 1·68	9·8 ± 1·65	8·8 ± 0·1	0·003	0·003	0·8	0·3
V1500 cGy (%)	17·6 ± 2·42	5·73 ± 1·24	4·2 ± 0·75	3·8 ± 0·52	0·002	0·0008	0·1	0·4

OAR, organ at risk; SD, standard deviation.

respectively). However, there is no significant difference between IMRT versus VMAT and VMAT versus VMAT-FFF in this regard.

IMRT and VMAT plans were superior with respect to brain sparing than the 3DCRT plans. The brain volumes receiving 500, 1,000 and 1,500 cGy were greatest with 3DCRT plans. Eldebawy et al. compared ten different treatment techniques for radiotherapy in three retinoblastoma patients and found that VMAT, staeriotactic radiotherapy and electron beam plans provided greatest sparing of brain.[23]

In this study, the VMAT and the IMRT plans had better conformity index as compared to the 3DCRT plans (3DCRT versus VMAT, $p = 0{\cdot}001$); however, no significant difference in CI was found between IMRT versus VMAT and VMAT versus VMAT-FFF plans. In a study by Vanetti et al., IMRT and VMAT plans were equivalent in terms of CI while in another study by Bertelsen et al., VMAT improved the CI compared with IMRT in treatment of head and neck cancers.[24,25]

In our study, the VMAT plans significantly reduced the MU delivery in comparison to the IMRT plans ($p = 0{\cdot}04$). This is consistent with previous studies.[20,16] Because of the delivery of more MUs and leakage of radiation in IMRT, there is increased potential of developing second malignancies in long-term survivors.[26]

The main limitation of our study is the small sample size. This is because there are few patients presents to us for radiotherapy.

Conclusion

The traditionally used anterior and lateral wedged portals negatively affect the dose distribution and OAR sparing. In our study, the VMAT and IMRT plans achieved statistically significant better target coverage than the 3DCRT plans and delivered less dose to the brainstem, optic chiasm and the brain. The use of VMAT-FFF beams did not show any benefit over VMAT in target coverage and OAR sparing. Although VMAT and IMRT showed mixed results on target coverage and OAR sparing, the VMAT plans were superior to the IMRT plans in respect to MU delivery. Moreover, VMAT delivered significantly lower dose to the brainstem and contralateral optic nerve. Therefore, VMAT should be used as the preferred external beam radiotherapy technique in the treatment of retinoblastoma. However, IMRT and VMAT should be used with caution because of increased low dose volumes to the contralateral lens and eyeball.

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Ethical Approval. The sudy was approved by Institutional Ethics Commitee.

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