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Dosimetric comparison of intensity-modulated radiation therapy and volumetric-modulated arc therapy plans for the treatment of glioma using flattening filter-free and flattening filter modes

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Abstract. In the present study, the dose verification between 6X and 6X flattening filter-free (FFF) in intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) was compared, and the advantages and disadvantages of different radiotherapy plans were evaluated. All four plans achieved comparable heterogeneity and conformity indices. For frontal tumor, VMAT demonstrated more improved sparing of the brainstem compared with the IMRT (P=0.045); while in the model of FFF, the Dmax of eye lens was significantly reduced by 16-21% (P<0.001). The organs at risk (OARs) in the temporal lobe tumor were spared well in the IMRT plan. With the removal of FF, the low-dose volume for both tumor locations was significantly reduced (P<0.05). By contrast, there was no significant difference in monitor units (MUs) with FFF, but the MUs were significantly reduced in the VMAT plan (P<0.001). Regarding the protection of OARs, FFF appeared to be superior compared with FF. For the frontal glioma, the VMAT plan had more advantages, and for temporal lobe tumor, dynamic IMRT was more appropriate. The VMAT plan reduces the low-dose volume of normal brain tissues and the MUs. While the removal of FF may increase the dose rate, the shortened treatment delivery time may improve the accuracy of treatment due to intra-fractional patient motion.

Introduction

Glioma is a type of tumor that originates from glial cells of the neuroderm (1). At present, postoperative radiotherapy is the standard treatment for high-grade glioma. Randomized controlled trials have demonstrated that postoperative radiotherapy prolongs the median survival time of patients from 3-6 months to 9-12 months (1). For glioma, intensity-modulated radiation therapy (IMRT) has been revealed to provide a more conformal dose distribution compared with conventional radiotherapy, with improved sparing of adjacent tissues (2-4).

Volumetric modulated arc therapy (VMAT) is a novel form of IMRT optimization that regulates the radiation dose with enhanced degrees of freedom, by continuously modulating the multi-leaf collimator (MLC) field shape, gantry rotation speed and dose rate. VMAT enables for additional flexibility in dose delivery and could further improve dose conformity and sparing of vital tissues. Compared with IMRT, the potential advantages of VMAT include a large reduction in treatment time and a concomitant reduction in the number of monitor units (MUs) required to deliver a given fraction size (5-9). It has been demonstrated that the removal of the flattening filter results in changes to the dose rate (10-13). Clinically, the MUs and dose rate increase with the use of flattening filter-free (FFF) beams and the treatment delivery time is reduced compared with IMRT (10-13).

A total of 21 patients with tumors located within the frontal lobe area (11 patients) and temporal lobe area (10 patients), who had been treated for tumor with radiotherapy at The First Affiliated Hospital of Zhengzhou University (Zhengzhou, China) between 2013 and 2014 were retrospectively selected. All patients had a pathological diagnosis of glioma. For each patient, four treatment plans, including a 6X-dynamic (d) IMRT, 6FFF-dIMRT, 6X-VMAT and 6FFF-VMAT plan were generated. The dose prescription was set to 60 Gy delivered over 30 fractions. The dose distributions for the planning target volume, organs at risk (OARs) and normal tissue were compared. The MUs were also evaluated. The dose distribution of target (Dmax, Dmin, Dmean, dose conformity and heterogeneity index), OARs (Dmax) and normal tissue (Dmean, V20Gy, V10Gy and V5Gy) were compared among the four plans.

Materials and methods

Patients. A total of 21 patients with glioma were selected from The First Affiliated Hospital of Zhengzhou University

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between September 2013 and August 2014 to be included in the present study. According to the World Health Organization classification, the clinical stages were as follows: Astrocytoma (stage II, n=5); oligodendroglioma (stage II, n=5); anaplastic astrocytoma (stage III, n=3); anaplastic oligodendroglioma (stage III, n=3); and glioblastoma (stage IV, n=5) (8). The exclusion criteria included any patient with abnormal function of heart, lung, liver and kidney (Karnofsky performance status <80). The median age was 43 years (range, 33-76 years), with 14 males and 7 males. For all patients, the location of glioma was in the frontal lobe area (11 patients) or temporal lobe area (10 patients).

For frontal lobe glioma, the largest beam field of planning target volume (PTV) was 11.5x13.5 cm^2 (range, 8x6.5-11.5x13.5 cm^2) and median PTV was 134.4 cm^3 (range, 59.5-364.5 cm^3). For temporal lobe glioma, the largest beam field of PTV was 11.5x9 cm^2 (range, 6.5x7-11.5x9 cm^2) and the median PTV was 109.7 cm^3 (range, 43.6-194.2 cm^3).

Definition and contour of targets. The target volume was delineated according to the no. 50 and 62 reports of the International Commission on Radiation Units and Measurements (8). For low-grade glioma, the gross tumor volume (GTV) was defined as the abnormal signal intensity area of T2-weighted-fluid-attenuated inversion recovery on a magnetic resonance imaging (MRI) scan, while a margin of 2.0 cm was added to the GTV to produce the clinical target volume (CTV). For high-grade glioma, the GTV was defined as the residual tumor and/or cavity of T1 on the MRI scan, and the CTV was defined as the GTV plus a margin of 3.0 cm. The CTV was expanded by 5 mm to produce the PTV.

Treatment planning. The treatment plans were generated using Eclipse™ 3D-TPS software (version 10; Varian Medical Systems, Palo Alto, CA, USA). dIMRT and VMAT plans were produced using 6-MV photons, and the dose prescription was set to 60 Gy in 30 fractions. The dose constraints to the OARs were determined using a Radiation Therapy Oncology Group protocol (6). The dIMRT plans consisted of six coplanar fields at gantry angles of 220˚. The VMAT plans consisted of a single arc, starting at a gantry angle of 179˚ and rotating counter-clockwise through 358˚ to stop at a gantry angle of 181˚, and another arc in the opposite direction. The two plans adopted the same approach during optimization. The upper limits of the dose rate for the 6X and FFF beams were 600 and 1,200 MU/min, respectively.

Dosimetric comparison. The dose volume histogram included the Dmax, Dmean and Dmin of CTV; and the Dmax, Dmean and Dmin of PTV. Conformity index was calculated as follows: $(PTV_{ref}/V_{PTV}) \times (PTV_{ref}/V_{ref})$ (14). Heterogeneity index (HI) was calculated as follows: D_5/D_{95}. To quantify the dose distribution on OARs and normal tissue (NT) at different dose levels, the percentage volume of the OARs and NT receiving a dose of 20, 10 and 5 Gy (V20, V10 and V5, respectively) were evaluated and compared.

Statistical analysis. Statistical significance was evaluated using a two-tailed Student's t-test. P<0.05 was considered to indicate a statistically significant difference. Analyses were performed using SPSS software (version 19.0; SPSS, Inc., Chicago, IL, USA).

Results

Frontal lobe glioma PTV coverage. In the same model, the Dmax and Dmean of CTV and PTV in dIMRT were increased compared with that in the VMAT plans (Table I). In the 6X, the Dmax and Dmean of CTV was 2.27 and 0.49%, respectively, and of PTV was 2.62 and 0.64%, respectively. In a model of 6FFF, the corresponding values were 1.58, 0.54, 1.75 and 0.59%, respectively. In the flattening filter (FF), the HI was more improved compared with the VMAT plans.

Traditionally, the FF in the X-ray beam path of a linear accelerator produces an almost uniform fluence over a collimated field. Based on these functions, the removal of the FF results in an increase in the dose rate and a decrease in radiation leak. Thus, in the FFF model, the dose distribution to a single field will be different from that of an FF beam (Fig. 1). The off axis response to dose distribution in the control group was similar in the 6X and FFF model (Fig. 1A), while the off axis responses in the experimental groups were significantly larger in the 6X model compared with the FFF model (Fig. 1B and C).

Integral dose to the OARs and NT. Compared with dIMRT, the VMAT plan significantly decreased the mean Dmax of the brainstem to 36% in the 6X (P=0.008), while the same index was 30% in the 6FFF model (P=0.045). In 6FFF-dIMRT, the mean Dmax decreased to 21% in the ipsilateral eye lens and 17% in the contralateral eye lens. Compared with 6X-VMAT, 6FFF-VMAT reduced the mean Dmax of the ipsilateral and contralateral eye lens to 16 and 10%, respectively (Table II).

Regarding the Dmean of NT, the 6X-dIMRT was increased compared with 6FFF-dIMRT, and the 6X-dIMRT was significantly increased compared with 6X-VMAT (P=0.013). No significant differences were identified in other groups. For the mean of low-dose of volume in NTs (V20Gy and V10Gy), the 6X-dIMRT was increased compared with 6X-VMAT, and compared with 6FFF-VMAT, the 6FFF-dIMRT was significantly increased (P<0.05). Among the four groups, there were significant differences in the mean of MUs. Compared with 6X-dIMRT, the group of 6X-VMAT decreased the mean of MUs from 543.9±29.78 to 414.7±18.29. The number of MUs for 6FFF-VMAT decreased by 19% compared with for 6FFF-dIMRT (Table III).

Temporal lobe glioma

PTV coverage. Under two different models, the mean of PTV's Dmin in dIMRT was reduced compared with the VMAT plan. The average value was 5,066.49±118.4 cGy and 5,333.67±88.79 cGy in 6X, while 5,113.98±100.47 cGy and 5,316.28±95.28 cGy in 6FFF. Regarding the HI, the 6FFF-dIMRT was increased compared with 6FFF-VMAT. The mean value was 1.050±0.0027 and 1.041±0.0023. No statistical differences were identified in other parameters.

Integral dose to the OARs and NT. In comparison to dIMRT, 6X-VMAT significantly increased the average value of Dmax

Table I. Comparison of dosimetric parameters of PTV, CTV, HI and CI.

Parameter	6X-dIMRT	6FFF-dIMRT	6X-VMAT	6FFF-VMAT	P-value
CTV, cGy					
Dmax	6,474.44±30.17	6,442.74±20.91	6,330.69±16.18	6,344.22±19.85	<0.001
Dmean	6,152.70±11.82	6,164.70±10.85	6,122.73±7.68	6,131.68±8.20	0.001[a]
Dmin	5,782.30±119.66	5,854.56±92.31	5,920.35±18.60	5,900.39±15.05	0.006[a]
PTV, cGy					
Dmax	6,532.77±34.95	6,506.39±30.62	6,365.63±19.35	6,394.85±20.01	<0.001
Dmean	6,150.95±9.85	6,154.30±8.93	6,111.22±6.00	6,118.94±6.07	<0.001[a]
Dmin	5,020.95±252.45	5,089.82±191.71	5,515.19±48.07	5,458.32±47.62	0.218
HI	1.051±0.0029	1.050±0.0025	1.032±0.0014	1.067±0.0326	<0.001[a]
CI	0.916±0.0048	0.922±0.0024	0.921±0.0028	0.925±0.0048	0.335

[a]Two-tailed P-values calculated using Wilcoxon matched-pair signed rank test. The parameters in 6X-dIMRT or 6FFF-dIMRT were compared with those in 6X-VMAT or 6FFF-VMAT. PTV, planning target volume; CTV, clinical target volume; HI, heterogeneity index; CI, conformity index; dIMRT, dynamic intensity-modulated radiation therapy; FFF, flattering filter-free; VMAT, volumetric modulated arc therapy.

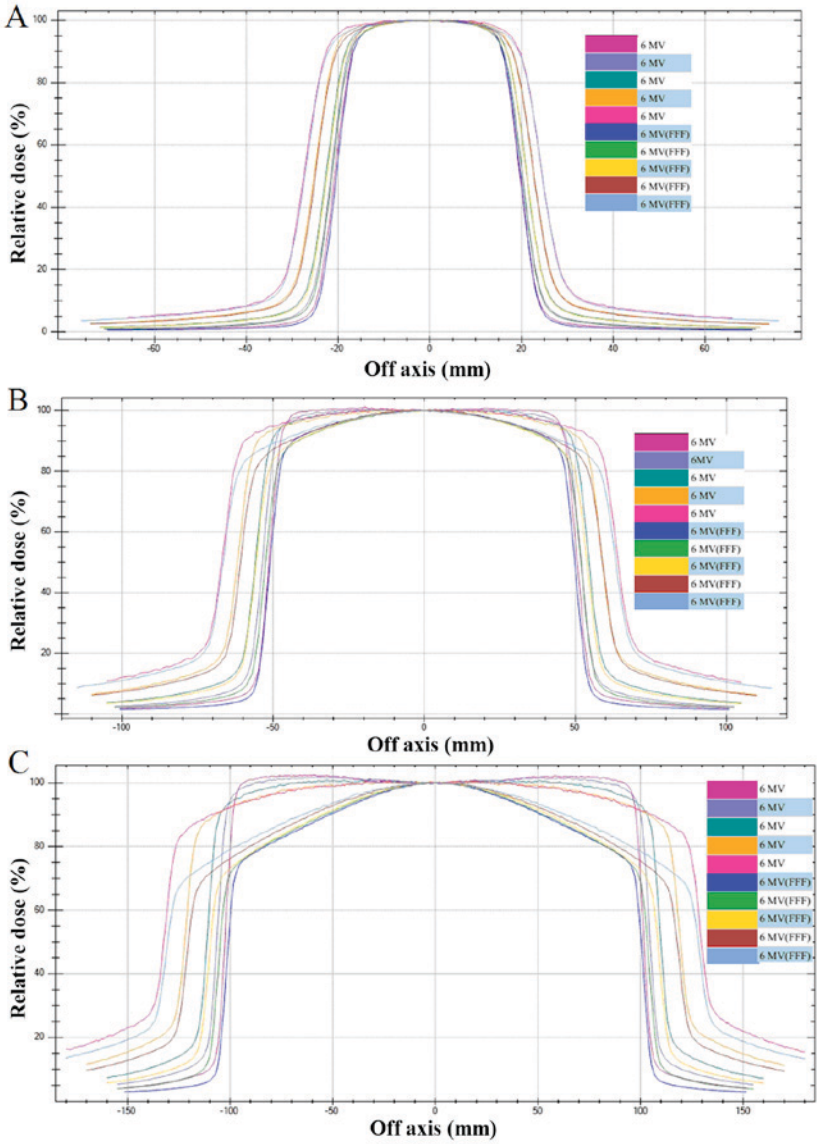

Figure 1. The off axis curve of 6X and FFF in different depths. (A) The off axis response to dose distribution in the control group was similar in the 6X and FFF model. (B and C) The off axis responses in the experimental groups were significantly larger in the 6X model compared with the FFF model. FFF, flattening filter-free.

Table II. Comparison of dosimetric parameters of organs at risk and normal tissue.

Parameter	6X-dIMRT	6FFF-dIMRT	6X-VMAT	6FFF-VMAT	P-value
Brainstem Dmax, cGy	1,838.13±508.77	1,711.94±463.59	1,174.82±311.91	1,188.24±323.59	0.001
Pituitary Dmax, cGy	820.50±353.48	843.42±376.29	961.63±475.67	957.14±480.44	0.162[a]
Lens-ips Dmax, cGy	276.03±67.43	218.31±52.58	245.62±58.40	214.97±54.61	<0.001[a]
Lens-cont Dmax, cGy	237.39±58.12	197.24±48.84	212.46±46.97	194.10±44.36	0.021
ON-ips Dmax, cGy	1,046.32±333.81	1,071.75±364.82	1,709.34±655.80	1,761.39±667.07	0.840[a]
ON-cont Dmax, cGy	648.60±217.87	640.32±229.76	926.66±358.32	884.28±351.54	0.782[a]
Chiasma Dmax, cGy	1,219.61±538.25	1,209.86±533.38	1,421.86±694.97	1,418.78±693.35	0.106[a]
TL-cont Dmax, cGy	1,719.79±454.25	1,697.98±444.88	1,706.99±478.26	1,486.35±472.11	0.203
Brain					
Dmean, cGy	788.88±102.17	780.53±102.7	772.62±104.14	771.04±106.71	0.003[a]
V20Gy, cm^3	673.85±84.12	667.25±83.56	625.99±90.76	621.50±92.94	<0.001
V10Gy, cm^3	1,048.81±118.52	1,024.69±118.65	1,076.32±124.07	1,064.28±126.42	<0.001
V5Gy, cm^3	1,503.2±105.09	1,480.34±108.02	1,490.86±107.5	1,477.09±108.59	0.171
MU	543.9±29.78	560.4±23.35	414.7±18.29	455.6±16.77	0.002[a]

[a]Two-tailed P-values calculated using Wilcoxon matched-pair signed rank test. The parameters in 6X-dIMRT or 6FFF-dIMRT were compared with those in 6X-VMAT or 6FFF-VMAT. Ips, ipsilateral; cont, contralateral; ON, optic nerve; TL, temporal lobe; MU, monitor units; dIMRT, dynamic intensity-modulated radiation therapy; FFF, flattering filter-free; VMAT, volumetric modulated arc therapy.

Table III. Comparison of dosimetric parameters of PTV, CTV, HI and CI.

Parameter	6X-dIMRT	6FFF-dIMRT	6X-VMAT	6FFF-VMAT	P-value
CTV, cGy					
Dmax	6,451.92±17.98	6,433.79±22.18	6,389.89±28.34	6,418.67±26.01	0.248
Dmean	6,164.94±9.62	6,177.13±10.35	6,054.71±93.71	6,163.13±9.85	0.138[a]
Dmin	5,760.52±118.36	5,784.79±115.23	5,797.90±78.30	5,785.88±75.23	0.664[a]
PTV, cGy					
Dmax	6,489.08±19.67	6,456.15±19.80	6,417.40±22.14	6,439.05±24.58	0.131
Dmean	6,155.03±8.01	6,160.96±8.73	6,131.84±6.45	6,145.86±8.24	0.052
Dmin	5,066.49±118.40	5,113.98±100.47	5,333.67±88.79	5,316.28±95.28	<0.001
HI	1.05±0.0023	1.050±0.0027	1.075±0.0376	1.041±0.0023	0.004[a]
CI	0.912±0.0105	0.918±0.0091	0.904±0.0067	0.905±0.0057	0.136

[a]Two-tailed P-values calculated using Wilcoxon matched-pair signed rank test. The parameters in 6X-dIMRT or 6FFF-dIMRT were compared with those in 6X-VMAT or 6FFF-VMAT. PTV, planning target volume; CTV, clinical target volume; HI, heterogeneity index; CI, conformity index; dIMRT, dynamic intensity-modulated radiation therapy; FFF, flattering filter-free; VMAT, volumetric modulated arc therapy.

and Dmean of the pituitary gland by 21% (P=0.012), while in the 6FFF-VMAT, the value increased by 19% (P=0.030). No statistical differences were identified in the other groups.

Regarding the bilateral lens, the mean of Dmax was significantly reduced in 6FFF-dIMRT compared with 6X (P<0.05). There was a reduction in the mean of Dmax of the ipsilateral lens in 6X-dIMRT (304.93±47.99 cGy) compared with 6FFF-dIMRT (283.45±43.96 cGy), with a simultaneous decrease in the value of the contralateral lens from 265.30±48.68 to 258.32±47.72 cGy.

The data revealed that the mean Dmax of the ipsilateral optic nerve was significantly reduced in 6FFF-dIMRT compared with that of 6FFF-VMAT (P<0.05). All values for the chiasma were compared in pairs, and the mean of Dmax of dIMRT was identified to be significantly decreased compared with VMAT in 6X and 6FFF (P<0.05). While compared with dIMRT, the plan of 6X-VMAT reduced the value of Dmax on the contralateral temporal lobe by 19%, and in the 6FFF model by 20%.

In the healthy brain tissue, the Dmean in 6X-dIMRT was increased compared with 6FFF-dIMRT, and the 6X-dIMRT was significantly increased compared with 6X-VMAT (P<0.001). No other statistical differences were identified. For the low-dose volume of NTs, the mean of V20Gy was increased

Table IV. Comparison of dosimetric parameters of organs at risk and normal tissue.

Parameter	6X-dIMRT	6FFF-dIMRT	6X-VMAT	6FFF-VMAT	P-value
Brainstem Dmax, cGy	2,619.63±510.16	2,617.22±514.88	2,333.51±489.88	2,370.47±502.15	0.484[a]
Pituitary Dmax, cGy	1,605.23±413.22	1,667.76±451.34	1,950.39±502.59	1,976.34±505.30	0.001
Lens-ips Dmax, cGy	304.93±47.99	283.45±43.96	314.69±46.79	307.36±46.05	0.024[a]
Lens-cont Dmax, cGy	265.30±48.68	258.32±47.72	290.01±47.46	300.42±52.40	0.039[a]
ON-ips Dmax, cGy	1,223.89±361.25	1,225.89±359.12	1,805.86±536.71	1,835.06±488.52	0.024[a]
ON-cont Dmax, cGy	627.95±122.62	643.67±130.22	870.37±191.30	826.98±165.04	0.068
Chiasma Dmax, cGy	1,601.55±471.82	1,594.55±472.96	2,112.10±596.47	2,129.90±585.43	0.042[a]
TL-cont Dmax, cGy	1,708.14±385.60	1,688.19±387.35	1,386.26±289.71	1,346.53±289.44	0.003
Brain					
Dmean, cGy	581.15±60.41	580.92±60.90	525.80±59.51	513.82±57.63	<0.001
V20Gy, cm^3	1,013.02±114.88	977.86±109.01	1,044.68±117.59	981.25±110.29	0.012[a]
V10Gy, cm^3	1,524.98±163.77	1,494.73±160.67	1,507.08±166.81	1,487.40±165.50	0.141
V5Gy, cm^3	562.7±26.24	583.8±28.66	450.0±24.93	469.2±22.56	<0.001
MU	581.15±60.41	580.92±60.90	525.80±59.51	513.82±57.63	<0.001

[a]Two-tailed P-values calculated using Wilcoxon matched-pair signed rank test. The parameters in 6X-dIMRT or 6FFF-dIMRT were compared with those in 6X-VMAT or 6FFF-VMAT. Ips, ipsilateral; cont, contralateral; ON, optic nerve; TL, temporal lobe; MU, monitor units; dIMRT, dynamic intensity-modulated radiation therapy; FFF, flattering filter-free; VMAT, volumetric modulated arc therapy.

in 6X-dIMRT compared with 6X-VMAT, and 6FFF-dIMRT was significantly increased compared with 6FFF-VMAT (P<0.05). For V10Gy in dIMRT, the model of 6FFF reduced the mean value from 1,013.02±114.88 to 977.86±109.01 compared with 6X. While in VMAT the 6FFF model reduced the mean value from 1,044.68±117.59 to 981.25±110.29.

Compared with 6X-dIMRT, the 6X-VMAT reduced the mean value of MUs from 981.25±110.29 to 450.0±24.93. The mean of MUs in 6FFF-VMAT was 469.2±22.56, which was reduced by ~20% compared with in 6FFF-dIMRT (583.8±28.66) (Table IV).

Discussion

Previous studies have suggested that the clinical application of FFF in prostate cancer or nasopharynx carcinoma improves the protection of the rectum and bladder (15,16). Considering the decreased dose to OARs and NT, FFF has an advantage over FF. The mean MUs were greater in the 6FFF model compared with 6X, which may be due to the softness of the rays. If the dose of the rays to deeper tissue is reduced, the MUs should be increased to reach the same depth.

During the process of VMAT the parameters, including the dose rate, the gantry rotation speed and the site of MLC change dynamically. Two types of products are currently in clinical use, Varian RapidArc and Elekta VMAT. As the application develops, the VMAT plan may become equal or superior to IMRT and tomotherapy. Compared with IMRT, the VMAT plan may increase the scattering of NTs, reduce the MUs and reduce the treatment duration (17,18).

In the current study, for frontal lobe glioma, the Dmax and Dmean of PTV in VMAT were increased compared with dIMRT, but no significant differences were identified in the OARs and NTs. For temporal lobe glioma, the protection of OARs, including pituitary gland, optic nerve and chiasma were more improved in the dIMRT plan compared with VMAT. The reason for this is primarily due to the spatial association between the location of the glioma and OARs. In an identical ray model, the differences in dose distribution to OARs between the two plans were not demonstrated to be statistically significant, as frontal lobe glioma is far from the lens and optic nerve. However, temporal lobe glioma is close to the OARs, and in certain patients, the tumor had invaded the edge of chiasma. The rotatory speed of the machine is constant at 4.8˚/s in the process of VMAT; the dose of adjacent field shape may be overlaid because of the speed of MLC, the positioning accuracy and the leakage ray, and as a result the Dmax of the pituitary gland and chiasma in VAMT was increased compared with dIMRT.

In the past few years, the VMAT plan has been gradually applied in clinical treatment. The FFF model provides a broad range of dose rates, and will be useful in the optimization of VMAT. However, simultaneously, the specialty of high dose rate in the FFF model complicates the regulation of the quality. In the future, as the speed of MLC increases, the high dose rate of FFF will be taken full advantage of. The VMAT plan should be reconsidered as the treatment duration may be reduced with use of the FFF beam or another technical innovation.

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