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Comparison of Flattening Filter and Flattening Filter-Free Volumetric Modulated Arc Radiotherapy in Patients with Locally Advanced Nasopharyngeal Carcinoma

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Background: This study aimed to investigate the therapeutic role of flattening filter-free (FFF) mode in volumetric modulated arc therapy (VMAT) compared with flattening filter (FF) mode in patients with locally advanced nasopharyngeal carcinoma (NPC).

Material/Methods: Ten previously treated patients with NPC underwent treatment re-planning with FFF and FF VMAT. Radiotherapy dose distribution on planning target volume (PTV), organs at risk (OAR), target conformity index (CI), total monitor units (MUs), and therapeutic time were compared.

Results: Maximum and mean radiotherapy dose in PTV and PGTV (primary lesions of NPC and cervical lymph node metastases) in FFF VMAT planning were significantly increased compared with FF VMAT planning, but PTV and OAR showed no significant differences. The CI value of PTV in FFF VMAT planning was significantly reduced compared with FF planning ($P<0.05$). No differences were found for the maximum radiotherapy dose in the spinal cord and left and right optic nerve, and the mean radiotherapy dose in the brainstem, left and right parotid gland ($P>0.05$). The maximum dose in the brainstem in the FFF planning was significantly higher compared with FF planning ($P>0.05$). The maximum radiotherapy dose in left and right crystalline lens ($P<0.05$) in FFF planning was significantly reduced compared with FF planning. The total hop count in FFF planning was significantly increased compared with FF planning ($P<0.05$).

Conclusions: Both 6 MV X-ray FFF mode and FF mode in the treatment of patients with NPC showed that FFF VMAT planning provided improved protection for OAR.

MeSH Keywords: **Epstein-Barr Virus Infections • Nasopharyngeal Neoplasms • Radiotherapy, Intensity-Modulated**

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Background

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy in the postnasal space. Risk factors for NPC include smoking and infection with Epstein-Barr virus (EBV), with a particularly high and increasing incidence of NPC reported in Southern China [1–4]. The overall rate of NPC in China has been reported to be more than 30 per 100,000 people [2,3]. EBV is a herpes virus that has oncogenic properties, and which is a significant risk factor for NPC [4]. In addition to EBV infection and smoking, the other environmental risk factors for NPC include dietary habits and exposure to toxic chemicals [5]. Because of its location, NPC often presents at a locally advanced stage, and early diagnosis significantly improves patient response to treatment and clinical outcome [4]. NPC is treated with surgery and local radiotherapy, and because of its location, it is necessary to control the dose and to carefully target the radiation to avoid damage to optic structures [6]. Therefore, it is important to design appropriate radiotherapy strategies for the treatment of locally advanced NPC.

Recently, volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy (IMRT) have become increasingly used treatment methods for many cancers, including esophageal cancer [7], gastric cancer [8], lung cancer [9], breast cancer [10], and NPC [11]. When compared with IMRT, VAMT technology has been shown to reduce the therapeutic time, reduce machine hop counts, and is associated with an enhanced tumor gain ratio [12–14]. Magnetic resonance imaging (MRI) has an important role in determining the extent of local tumor invasion and metastases and patient prognosis and outcomes following IMRT treatment in NPC [15]. Also, diffusion-weighted imaging has been extensively applied in the evaluation of the cancers, such as NPC, head and neck cancers, to evaluate the spread of the tumor, and the clinical response to therapy [16].

In conventional VAMT, the flattening filter (FF) is used, but is associated with some disadvantages, as the FF prolongs the on-beam times, causes lower treatment doses, decreases the photon intensity and enhances the degree of scatter of the treatment dose [17,18]. Recently, the in VAMT, the use of flattening filter-free (FFF) beams have been investigated [19–21]. Zwahlen et al. [22] reported that the FFF beams could provide a solution to minimize the whole-body dose of the radiotherapy when combined with VMAT technology. Alongi et al. [23] found that the application of FFF beams could significantly decrease acute radiation toxicity when combined with the VMAT technology.

Many factors can affect the application of VMAT in patients with NPC, including the large planning target volume (PTV), the proximity of vital normal tissues, which make the planning of radiation treatment of NPC cases challenging [24]. Therefore, the aims of the present study were present study were to investigate the therapeutic role of the flattening filter-free (FFF) mode in volumetric modulated arc therapy (VMAT) compared with the flattening filter (FF) mode in patients with locally advanced nasopharyngeal carcinoma (NPC). The study also aimed to examine the differences between the PTV and the organs at risk (OAR) between the two types of radiation beam.

Material and Methods

Patients

Ten patients with locally advanced nasopharyngeal carcinoma (NPC) were included in the study. All patients were treated in the Department of Radiation Oncology in the First Affiliated Hospital of Zhengzhou University. The age of the patients ranged from 23–59 years, with a median age of 40 years. Patients were staged according to the 2002 Union for International Cancer Control (UICC) staging guidelines and included patients with a clinical stage of III–IVb. According to the TNM staging system, two cases were diagnosed as stage T2, six cases were diagnosed as stage T3, two cases were diagnosed as stage T4. Also, four cases were diagnosed as stage N2, and six cases were diagnosed as stage N3.

All patients included in the study provided written informed consent. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

Planning target volume (PTV) and treatment doses used in volumetric modulated arc therapy (VMAT)

In this study, two planning targeting volumes (PTVs) were used: the PGTV, the targeting volume in the primary lesion of NPC and cervical lymph node metastases, which were given 70 Gy in the 33 fractions; and the PTV, the tumor and the areas surrounding the primary tumor and the drainage areas of the middle and lower cervical lymph nodes, which were given 60 Gy in the 33 fractions.

Volumetric modulated arc therapy (VMAT) treatment planning

The VMAT treatment plans assigned non-coplanar 6 MV flattening filter-free (FFF) beams and conventional flattening filter (FF) beams, which were delivered by the TrueBeam linear accelerator (Varian Medical System Inc., Palo Alto, CA, USA), and the Eclipse™ treatment planning system. In the PTV and PGTV treatment planning for the patients with NPC, planning confirmed that 95% of the PGTV and PTV received the prescribed dose of 70 Gy and 60 Gy, respectively. The optimization objectives

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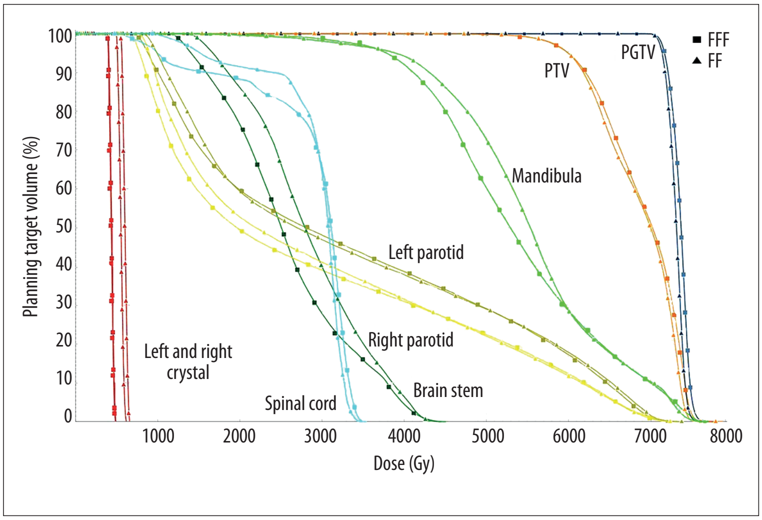

Figure 1. The radiotherapy dose-planning target volume histogram in flattening filter-free (FFF) volumetric modulated arc therapy (VMAT) planning and filter-free (FF) VMAT planning.

were adjusted to confirm that no more than 1% of the PTV was below the 110% of the prescribed dose [25]. The quantity of radiation delivered to organs at risk (OAR) included: crystalline lens D_{max} <9 Gy; brainstem D_{max} <54 Gy; spinal cord D_{max} <40 Gy; parotid glands D_{max} <30 Gy; optic nerve D_{max} ≤54 Gy.

The VMAT planning adopted the fixed lead door co-planar double arc irradiation: the first arc of irradiation was counterclockwise from 179° to 181°; the second arc of irradiation was in the opposite direction, and the total arc was 716°. The maximum dose for the FFF beams and FF beams were 800 monitor units (MUs)/min and 600 MUs/min, respectively. The final treatment dose was calculated by using the Anisotropic Analytical Algorithm (AAA) (version 10.0.28), with a grid size of 0.2 cm.

Plan evaluation

The volume histogram, dose distribution, maximum dose, minimum dose, mean dose and conformity index (CI) were used as the comparators between the FFF planning and FF planning. The CI used to assess the dose conformity was assigned as the following [26]:

$$CI=\frac{PTV_{ref}}{V_{PTV}}\times\frac{PTV_{ref}}{V_{ref}}$$

Where the PTV_{ref}, V_{PTV}, V_{ref} represent the 95% prescribed dose of PTV, PTV volume, 100% prescribed dose of PTV, respectively. The maximum dose for the brainstem, crystalline lens of the eye, spinal cord, and optic nerve was evaluated, and mean dose for parotid gland, and total irradiated areas was also evaluated. The machine hop count was assigned as the sum of the hop counts of the two VMAT planning irradiation arcs. The therapeutic time was assigned as the time used by the Varian TrueBeam linear accelerator.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) and analyzed by using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA). The Student's t-test was used to analyze the differences between the FFF beams and FF beams. P-values <0.05 were considered to be statistically significant.

Results

Volume histogram for radiotherapy dose in the volumetric modulated arc therapy (VMAT) modes

To evaluate the radiotherapy dose in the ten patients with nasopharyngeal carcinoma (NPC) treated with volumetric modulated arc therapy (VMAT) in the planning target volume (PTV) and organs at risk (OAR), the planning target volume histogram for two planning beams was drawn. The results showed that the majority of the targeting volume and the OAR showed no significant differences for radiotherapy dose between the FFF VMAT planning and FF VMAT planning (Figure 1). However, the maximum radiotherapy dose in FFF VMAT planning was significantly less compared with the FF VMAT planning (Figure 1) ($P<0.05$).

Comparison of the radiotherapy dose in planning target volumes (PTVs) in VMAT modes

The results showed that both the maximum radiotherapy dose ($t=-3.06$) ($P<0.05$) and the mean radiotherapy dose ($t=-1.29$) ($P<0.05$) of PGTV (PTV for primary lesions of NPC and cervical lymph node metastases) in FFF VMAT planning was significantly higher compared with FF VMAT planning (Table 1). However, the maximum radiotherapy dose ($t=-3.06$) ($P<0.05$) and mean radiotherapy dose ($t=-3.53$) ($P<0.05$) of PTV in FFF VMAT planning was significantly higher compared with FF VMAT

Table 1. Radiotherapy dose comparison for the planning target volume (PTV) of primary lesions of nasopharyngeal carcinoma (NPC) and the PGTV (NPC including cervical lymph node metastases) between the flattening filter-free (FFF) beams and flattening filter (FF) beams (cGy, $\chi^2 \pm s$).

Planning	PGTV D_{max}	PGTV D_{min}	PGTV D_{mean}	PGTV CI	PTV D_{max}	PTV D_{min}	PTV D_{mean}	PTV CI
FFF	7831±134	7396±94	6600±329	0.48	7838±133	4180±445	6821±88	0.81
FF	7709±138	7396±94	6566±367	0.45	7716±138	4133±449	6767±62	0.83
t value	−3.06	−3.77	−1.29	2.11	−3.06	−0.44	−3.53	5.42
P value	0.01	0	0.23	0.06	0.01	0.67	0.01	0

FFF – flattening filter-free; FF – flattening filter; PTV – planning target volume; PGTV – PTV for primary lesions of NPC and cervical lymph node metastases; NPC – nasopharyngeal carcinoma; CI – target conformity index; D_{max} – maximum radiotherapy dose; D_{min} – minimum radiotherapy dose; D_{mean} – mean radiotherapy dose.

Table 2. Radiotherapy dose comparison for the organs at risk between the flattening filter-free (FFF) beams and flattening filter (FF) beams (cGy, $\chi^2 \pm s$).

Planning	Brain stem D_{max}	Spinal cord D_{max}	Left crystal D_{max}	Right crystal D_{max}	Left optic nerve D_{max}	Right optic nerve D_{max}	Left parotid D_{max}	Right parotid D_{max}	Whole therapeutic area
FFF	4575±248	3569±173	488±59	488±71	5482±491	5557±261	2901±493	2928±116	1921±374
FF	4499±226	3567±183	605±57	611±72	5401±457	5337±470	2924±514	2926±422	1935±372
t value	−5.57	−0.1	25.87	17.45	−2.15	−2.04	0.48	−0.04	1.47
P value	0.00	0.92	0.00	0.00	0.06	0.07	0.64	0.97	0.18

FFF – flattening filter-free; FF – flattening filter; D_{max} – maximum radiotherapy dose.

planning (Table 1). There were no significant differences for minimum radiotherapy dose between PGTV and PTV and for the CI value of PGTV between FFF VMAT planning and FF VMAT planning (Table 1). The CI value of PTV in FFF VMAT planning was significantly lower compared with the FF VMAT planning (t=5.42) (P<0.05) (Table 1).

Comparison of the radiotherapy dose for organs at risk (OAR)

There were no significant differences between the maximum radiotherapy dose in the spinal cord and left and right optic nerve, and mean radiotherapy dose in the brainstem, the left and right parotid gland, and the whole treatment areas, between the two VMAT planning modes (P>0.05) (Table 2). However, the maximum radiotherapy dose in the brainstem in FFF VMAT planning was significantly higher when compared with FF VMAT planning (t=–5.57) (P>0.05) (Table 2). The maximum radiotherapy dose in the left crystalline lens (t=25.87) (P<0.05) and right crystalline lens (t=17.45) (P<0.05) in FFF VMAT planning were significantly lower compared with FF VMAT planning (Table 2).

Comparison of the total hop count and therapeutic time in the two planning modes

The total machine hop count in FFF VMAT planning (699±16 MU) was significantly higher compared with FF VMAT planning (628±12 MU) (t=16.54) (P<0.05) (Figure 2A). However, there were no significant differences in the mean therapeutic time between the two VMAT planning procedures (P>0.05) (Figure 2B).

Discussion

The main aim of the present study was to evaluate the potential application of the flattening filter-free (FFF) mode of a linear accelerator for volumetric modulated arc radiotherapy (VMAT) in patients with locally advanced nasopharyngeal carcinoma (NPC), and compared the radiotherapy dose between the FFF VMAT planning and the flattening filter (FF) VMAT planning. The findings showed that there were no significant differences for the minimum radiotherapy dose in planning target volume (PTV) and PGTV (primary lesions of NPC and cervical lymph node metastases), and for the target conformity index (CI) value of PGTV between FFF VMAT and FFF VMAT planning. However, there were significant differences between the

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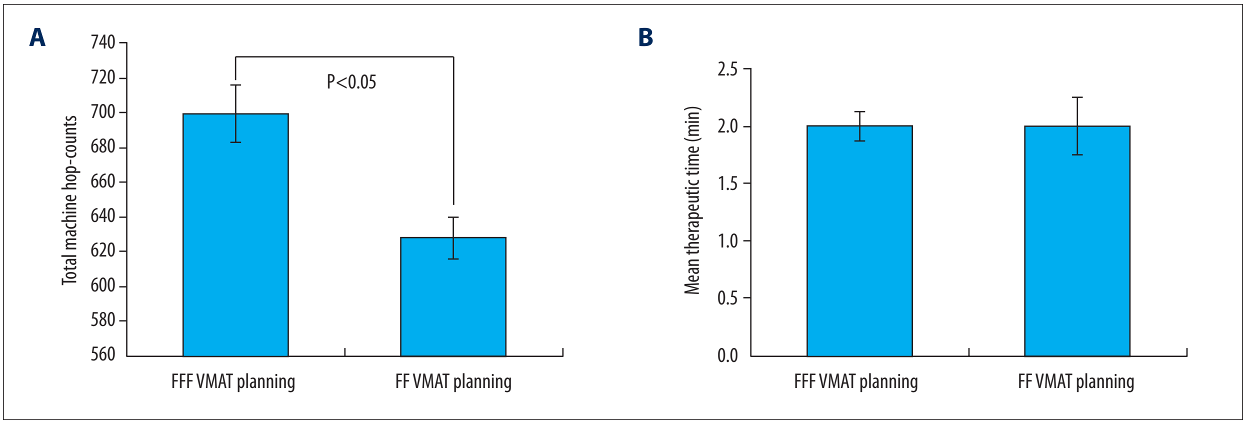

Figure 2. Total hop count and therapeutic time in flattening filter-free (FFF) and filter-free (FF) volumetric modulated arc therapy (VMAT) planning. (**A**) The total machine hop count in flattening filter-free (FFF) and filter-free (FF) volumetric modulated arc therapy (VMAT) planning. (**B**) The mean therapeutic time in two rounds of VMAT planning. * $P<0.05$ represents the total machine hop count in FFF VMAT planning compared with FF VMAT planning.

maximum and mean radiotherapy dose in PGTV and PTV between the two planning modes. These differences might have been caused by the removal of the flattening filter in the FFF mode, and its replacement by the thin copper sheeting [27]. In the FFF mode, the beams were soft, and the radiation dose was close to a 4 MV FFF beam, which results in a lower accumulation of the radiotherapy dose in the FFF mode compared with the FF mode [27].

According to the degree of invasion of NPC and the depth of the tumor from the body surface, the FFF mode in this study appeared to output more machine hop counts to ensure the radiotherapy dose reached the required depth in the tissues. For this reason, the radiotherapy dose accumulation in the target volumes was significantly higher in the FFF mode compared with the FF mode. Therefore, the maximum and mean radiotherapy dose in the target volume was higher in the FFF mode compared with the FF mode. Also, the conformity index (CI) in the FFF mode was significantly lower compared with the FF mode, which may be due to the more rapidly reduced off-axis dose and lower beam energy, which might make it more difficult for the radiotherapy dose to achieve the required depth of the target volume. The findings of this study are supported by previous studies, which have investigated the FFF mode in other diseases [28,29]. Also, magnetic resonance imaging (MRI) has previously been used routinely to investigate the activity and safety of preoperative radiation treatment of head and neck cancers [16,30]. In the present study, diffusion-weighted MRI was also used to evaluate NPC.

There were no statistically significant differences between radiotherapy dose in the majority of organs at risk (OAR) between the FFF planning and FF planning groups, including the brainstem, and although maximum dose was higher in FFF compared with FF planning, there was no statistically significant difference in dosing of most of the OARs. However, the mean radiotherapy dose in the left and right crystalline lens in FFF planning was significantly lower compared with FF planning, which may be caused by the more rapid drop in axis dose, reduced out of volume dose, reduced beams, and decreased the radiation dose of the multi-leaf collimator (MLC) in the FFF mode [31]. A previously published study [32] reported that the crystalline lens of the eye is particularly sensitive to the radiation damage. Therefore, the lower radiation triggered by the FFF mode might decrease the radiation risk to the left and right crystalline lens.

In this study, the range of radiotherapy dosing in the FFF beams was between 0–800 MUs/min and 0–600 MUs/min in FF beams. According to the actual dose, the dose in the FFF mode was 350 MUs/min and 320 MUs/min in the FF mode. The findings from a previous study showed that the maximum dose that FFF beams could achieve was up to 1400 MUs/min [33]. Although in the present study, the FFF mode did not include the maximum dose of 1400 MUs/min, which did not affect the results. Also, in the present study, the total machine hop count in FFF VMAT planning was significantly higher compared with the FF VMAT planning, which was a finding supported by a previous study by Zwahlen et al. [22]. In a previously published study, Fu et al. reported that the difference in the therapeutic time between the FFF mode and FF mode was associated with a single therapy dose [34]. The findings from the present study showed that there was no difference in the mean therapeutic time between the two VMAT planning modes. Because a larger radiation dose always triggers a shorter therapeutic time, a 2.12 Gy single dose was used in both the FFF mode and FF mode, resulting in no significant difference for the therapeutic time between the two modes.

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Conclusions

Both of the volumetric modulated arc radiotherapy (VMAT) procedures, including the flattening filter-free (FFF) mode and the flattening filter (FF) mode, have previously been shown to be suitable for the treatment of patients with locally advanced nasopharyngeal carcinoma (NPC). The findings of this study showed that FFF VMAT planning could better protect the organs at risk (OAR) surrounding the planning target volume (PTV), including the left and right crystalline lens of the eye.

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