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A Dosimetric Comparison of HyperArc Therapy Planning and Volumetric Modulated Arc Therapy Planning in Treating Patients With Glioblastoma Multiforme

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Abstract

Background/Aim: This study aimed at evaluating the potential benefit of automatic non-coplanar volumetric arc therapy (VMAT) (hyperarc, HA) technique in treating glioblastoma multiforme (GBM).

Patients and Methods: Twenty-seven patients with GBM who received coplanar VMAT (C-VMAT) were selected in this study. HA and non-coplanar VMAT (NC-VMAT) plans were generated with the same prescriptions and constraints. The Target coverage, organs at risk (OARs) dose, and dosimetric indexes were compared among three plans.

Results: The HA plan demonstrated a reduction in dose to normal tissues while maintaining target coverage, compared to C-VMAT and NC-VMAT. Additionally, HA plans demonstrated higher coverage of the GTV and PTV_{60} as well as improved CI from PTV_{60} and PTV_{46} compared to the other plans. Regarding the dose gradient, HA plans showed a greater dose fall-off, resulting in reduced high-dose and intermediate-dose spillage at PTV_{46}. The HA also demonstrated a tighter gradient radius at PTV_{60} and PTV_{46}. The HA plan requires fewer MUs than both C-VMAT and NC-VMAT.

Conclusion: The HA plan had better dosimetric results compared to C-VMAT and NC-VMAT. The HA with automatic planning module and auto-delivery treatment also provided high-quality planning and delivery efficacy. These advantages suggest that HA could potentially escalate tumor doses while minimizing toxicity, thereby improving outcomes in GBM patients.

Keywords: Glioblastoma multiforme, HyperArc, volumetric arc therapy, dosimetric quality, adjacent organs at risk.

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Introduction

Glioblastoma multiforme (GBM), also referred to as a grade IV astrocytoma, is recognized as the most common and aggressive type of primary brain tumor (1). The current standard management of GBM includes extensive surgery followed by radiation therapy (RT) plus concomitant and adjuvant temozolomide (2). Regardless of the type of multidisciplinary comprehensive care, the survival rate remains poor, with a median survival time of only 15 months (3). Due to shortened life expectancy, there is a growing focus on enhancing quality of life, particularly concerning cancer and its treatment, among these patients (4). Instead of typical acute toxicities such as fatigue, dermatitis, alopecia, dizziness, and headache, late toxicity includes neurological dysfunction and cognitive deficits which may also affect patients' quality of life. Thus, important treatment goals for patients with GBM include optimal dose delivery to the tumor target and limited exposure to adjacent normal structures during radiotherapy (5).

In recent decades, advancements in RT techniques have been notable. Technical innovations such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic radiosurgery (SRS) have emerged, aiming to preserve more normal tissue and mitigate potential long-term toxicity while maintaining treatment efficacy for brain tumors (5-7). Scaringi *et al*. indicated that IMRT and VMAT techniques have the potential to facilitate escalated tumor doses or hypo-fractionated radiation schedules without increasing toxicity to normal tissue, thereby potentially enhancing local tumor control and improving survival rates among patients with brain tumors (5). Whether applied to low-grade or high-grade gliomas, IMRT and VMAT facilitate improved target conformity and enhanced sparing of critical tissues such as the hippocampus and brainstem, potentially mitigating late toxicities associated with RT (5, 6, 8, 9).

Recently, a novel treatment technique known as HyperArc (HA) has been introduced. This innovative approach offers automated settings for isocenter placement, non-coplanar beam arrangement, and collimator angles. By leveraging these features, HA delivers a highly conformal dose to the target while minimizing radiation exposure to surrounding tissues to the greatest extent possible (10-13). Additionally, radiation therapists are not required to enter the treatment room due to the automated couch rotation movement during treatment, which effectively reduces treatment duration. Many studies have shown that the HA plan is dosimetrically superior to the conventional VMAT plan for the treatment of brain metastases and other head and neck lesions, with significantly higher conformity and rapid dose falloff (14-19). Pan *et al.* reported their experience with the use of HA therapy in boost radiotherapy for single GBM, demonstrating that HA plans offer better conformity and sparing of normal organs (20). However, the dosimetric advantages of HA adapted for the entire course of GBM irradiation remain insufficiently explored.

This study was designed to evaluate the potential benefit of HyperArc used for GBM treatment. The tumor coverage, dose to adjacent organs at risk (OARs) and dosimetric parameters of HA, were compared with coplanar volumetric arc therapy (C-VMAT), and non-coplanar VMAT (NC-VMAT) plans in this study.

Patients and Methods

Study patients and characteristics. Twenty-seven patients with GBM who had received C-VMAT from 2012 to 2022 were selected in this study. All patients received surgery or stereotactic biopsy before RT. Retrospective dosimetric comparisons were made by creating NC-VMAT and HA plans for each patient. A total of 27 patients with GBM were selected for analysis: 17 males (63%) and 10 females (37%). The mean age at diagnosis was 60 years (range=34-78 years). For tumor location, 14 patients had right side, 13 patients had left side cancer. For all patients, the prescribed doses were 46 Gy in 23 fractions to the planning target volume (PTV_{46}), followed by a boost to

PTV_{60} with 14 Gy in seven fractions, resulting in a total cumulative dose of 60 Gy in 30 fractions. The median values of gross tumor volume (GTV), clinical target volume (CTV), PTV_{60} and PTV_{46} were 37.08, 244.80, 173.50, and 385.60 cm^3, respectively.

Contouring and treatment plan criteria. All patients were immobilized in a supine position with a thermoplastic mask (Pre-molded U-Frame mask, made from Blessing Cathay Corporation, New Taipei City, Taiwan, ROC). Computed tomography (CT) simulations were performed with a Toshiba big bore 16 slice CT scanner (Canon Medical System, Otawara, Japan). CT slice thickness was 3-mm with matrix size of 512 by 512 pixels. At our institution, following the Radiation Therapy Oncology Group (RTOG) and National Comprehensive Cancer Network (NCCN) guidelines, the treatment planning CT-scan was fused with a pre- and/or post-operative magnetic resonance imaging (MRI) to delineate target volumes. The GTV was delineated as the volume encompassing the resection cavity and regions delineated by gadolinium contrast-enhanced T1-weighted MRI images (Discovery MR 750, GE medical system, GE Healthcare, Chicago, IL, USA). The CTV extended isotropically by 1.5-2 cm from the GTV, with adaptations made to encompass areas displaying fluid-attenuated inversion recovery (FLAIR) abnormalities on fused MRI images suggestive of potential tumor infiltration, while adhering to normal anatomical boundaries. Both the CTV and GTV were expanded by 0.3-0.5 cm to create the PTV_{46} and boost PTV_{60}, respectively. According to the guidelines from the Radiation Therapy Oncology Group (RTOG) 9710, the prescribed total cumulative dose was 60 Gy, administered at 2 Gy per fraction in two phases of prescription (46 Gy initially, followed by a boost of 14 Gy) (21). The tumor coverage was determined by the proportion of the target volume that received 100% of the prescription dose. The OARs included the brainstem, optic apparatus (including eyes, optic nerves, chiasma, and lens) and normal brain (brain minus PTV_{46}). A minimum of 100% of the prescription dose was assumed to cover 95% of the PTV volume. The dose constrains of critical normal organs included brainstem (maximum dose <54 Gy) and optic apparatus (chiasm, optic nerves <50 Gy, lens <8 Gy). The dose to the normal brain was as low as possible. The priority of the planning goal was sparing of OARs, followed by target coverage. The V_x of normal brain represents the volume receiving greater than or equal to a dose of x Gy.

CT data sets and target volume/normal organ contours from the 27 patients with GBM were re-planed in the Eclipse treatment planning system (Version 15.5, Varian Medical Systems, Palo Alto, CA, USA), using beam data from the TrueBeam linear accelerator (Varian Medical Systems). The TrueBeam linear accelerator features a 120-leaf high-definition multi-leaf collimator (MLC) with dynamic beam aperture, boasting a spatial resolution of 2.5 mm leaf width ×32 pairs at the center and 5 mm width ×28 pairs in the peripheral leaves. Additionally, it offers a maximum static field size of 40 cm×22 cm.

HA, C-VMAT and NC-VMAT plans were generated in accordance with the same dose prescription and OAR constraints. For HA plans, virtual support structures including the Encompass device and QFix mask (CQ Medical, Avondale, PA, USA) were inserted into the CT image. The HyperArc plan module automatically selected most of beam parameters. The isocenter was automatically positioned at the center of the selected target structures using HyperArc plan template. Collimator angle and field size were optimized to minimize OAR dosages. Additionally, beam geometry (gantry, collimator, and couch angles) was automatically selected, comprising one full or half coplanar arc with a couch rotation of 0˚ and up to three partial noncoplanar arcs with couch rotations of 315˚, 45˚, and 90˚ (or 270˚). SRS normal tissue objective (NTO) was applied during HA optimization. SRS NTO, a dose fall-off tool that can be only used in HA, generates a virtual shell structure to decrease the dose outside the target volume. Six MV flattening filter-free (6FFF) photon beams with a dose rate of 1,400 monitor units (MU)/min were employed for all plans.

The isocenter and beam energy of HA were used in the C-VMAT and NC-VMAT plans. Two partial coplanar arcs

(Rt partial arc: gantry from 50˚ to 181˚ and rotation back; Lt partial arc: gantry from 300˚ to 179˚ and rotation back, collimator angle was 5˚ and 355˚) were applied for C-VMAT treatment plans. The same two partial coplanar-arcs used in C-VMAT plan and one vertex non-coplanar partial arc (couch 90˚ or 270˚, gantry from 179˚ to 30˚, collimator angle was 0˚) were used to generate NC-VMAT plans. The beam arrangements are illustrated in Figure 1. Automatic NTO was used in C-VMAT and NC-VMAT plans during plan optimization. Automatic NTO has a separate internal set of parameters that depend on the distance from the target. The dose calculations model was performed using the Anisotropic Analytical Algorithm (AAA, Version 15.5.12, Varian Medical Systems) with a 2.5 mm dose grid size. The jaw tracking option was applied to C-VMAT and NC-VMAT plans. The optimization parameters of initial and boost plans are listed in Table I.

Plan evaluation statistics and dosimetric parameters. To assess the plan quality, dosimetric parameters included target coverage, OAR dose, and dosimetric indexes (Paddick conformity index, homogeneity index, and dose gradient). $D_{2\%}$ (the dose to 2% of the volume) was utilized to assess near-maximum dose for both CTV and PTV, while $D_{98\%}$ evaluated near-minimum dose. The CIs of PTV_{60} and PTV_{46} were used to evaluate the dose conformity in total dose prescription. The Paddick conformity index (CI) was defined as:

$$CI = \frac{TV_{PIV}^2}{TV \times PIV}$$

where TV_{PIV} represents the target volume covered by the prescription isodose volume, TV denotes the target volume, and PIV signifies the prescription isodose volume (22). A higher CI indicates superior plan conformity, with a CI value of 1 representing ideal conformity. The homogeneity index (HI) was calculated as follows:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$$

An HI of zero indicates near-homogeneous distribution of absorbed dose within the target (23). Dose spillage was introduced to depict the dose falloff beyond the target. Lower isodoses outside the PIV may encompass substantial amounts of normal tissues, potentially leading to complications, particularly when the target is near critical structures. To assess dose falloff outside the target, the evaluated metrics include intermediate dose spillage, high dose spillage, and gradient radius (24-26). Intermediate dose spillage was calculated as:

$$\text{Intermediate dose spillage} = \frac{\textit{the volume receiving } 50\% \textit{ of prescription dose}}{\textit{PTV volume}}$$

High dose spillage was calculated as:

$$\text{High dose spillage} = \frac{\textit{the volume of } 105\% \textit{ isodose volume outside the PTV}}{\textit{PTV volume}}$$

The gradient radius, measured in centimeters, was determined by subtracting the equivalent sphere radius of the volume covered by 50% of the prescription isodose curve from the equivalent sphere radius of the prescription isodose volume. A smaller gradient radius signifies minimal dose dispersion beyond the lesion and a steep dose falloff (27).

$$Gradient\ Radius = \sqrt[3]{\frac{3V_{50\%}}{4\pi}} - \sqrt[3]{\frac{3V_{100\%}}{4\pi}}$$

Ethics approval and consent to participate. The research received approval from the Ethics Committee of the Institutional Review Board (IRB) at Chi Mei Medical Center (IRB: 11105–013) and adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was not acquired, as the IRB waived the requirement for individual consent due to the absence of personally identifiable information. All data were analyzed in a confidential and anonymous manner.

Statistical analysis. The dosimetric endpoints of the target volumes and OARs, CI, HI, intermediate and high dose spillages, gradient radius and monitor unit (MU), were

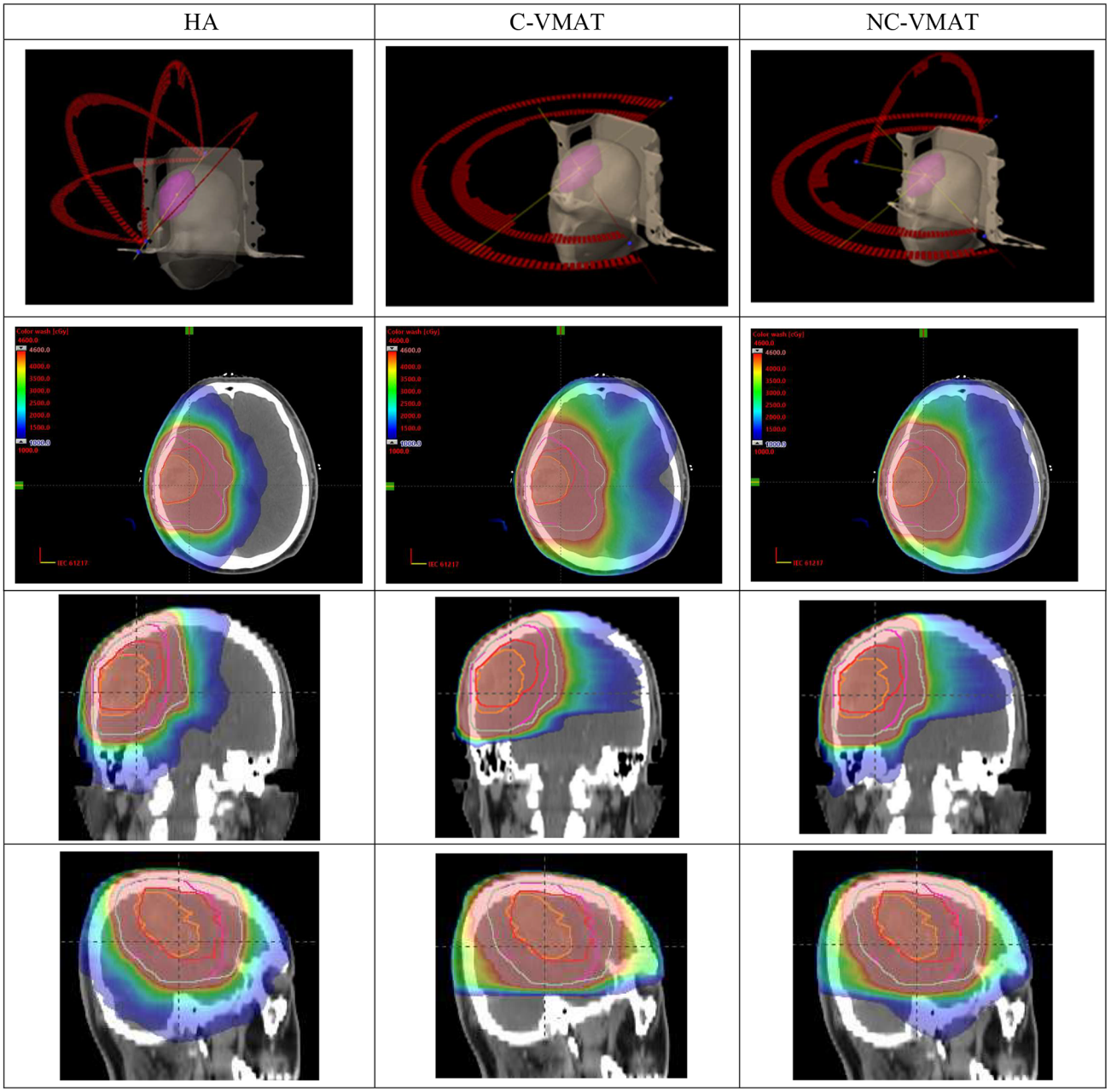

Figure 1. *Comparison of the beam arrangement and dose distribution between HyperArc (HA), coplanar volumetric arc therapy (C-VMAT), and non-coplanar VMAT (NC-VMAT) plans. The orange color represents the gross tumor volume (GTV), red indicates the clinical target volume (CTV), magenta corresponds to planning target volume with prescribed doses to 60 Gy (PTV60), and light green denotes planning target volume with prescribed doses to 46 Gy (PTV46).*

subjected to analysis using the *t*-test (SPSS Statistics, Version 19, IBM, Armonk, NY, USA). All tests were two-tailed, and Post Hoc tests with ANOVA were additionally employed for comparisons among the HA, C-VMAT, and NC-VMATN groups. A *p*-value less than 0.05 was deemed statistically significant.

Table I. *Optimization parameters for initial and boost plans.*

	Type	Volume (%)	Dose (cGy)	Priority
Initial plan	PTV46	100	4,600	125
		0	4,750	125
	Brain stem	0	4,650	110
	Chiasma	0	4,650	110
	Normal brain	mean	1,000	110
	Contralateral optic nerve	0	4,000	105
	Ipsilateral optic nerve	0	2,000	110
	Contralateral eye	0	3,000	105
	Ipsilateral eye	0	1,500	110
	Contralateral lens	0	600	115
	Ipsilateral lens	0	100	115
	SRS NTO (HA)			125
	Automatic NTO (C-VMAT, NC-VMAT)			125
Boost plan	PTV60	99.9	1,200	125
		0	1,250	125
	Brain stem	0	600	110
	Chiasma	0	600	110
	Normal brain	mean	200	110
	Contralateral optic nerve	0	600	105
	Ipsilateral optic nerve	0	200	110
	Contralateral eye	0	300	105
	Ipsilateral eye	0	200	110
	Contralateral lens	0	80	115
	Ipsilateral lens	0	80	115
	SRS NTO (HA)			125
	Automatic NTO (C-VMAT, NC-VMAT)			125

PTV60: Planning target volume prescribed to 60 Gy; PTV46: planning target volume prescribed to 46 Gy; C-VMAT: coplanar volumetric arc therapy; NC-VMAT: non-coplanar volumetric arc therapy; HA: HyperArc.

Results

Target coverage. The target coverage is listed in Table II. HA plans show slightly higher target coverage in GTV and PTV_{60} than VMAT and NC-VMAT. The GTV coverage was 99.54, 98.98, and 99.38% for the HA, C-VMAT, and NC-VMAT. The PTV_{60} coverage was 97.27, 96.34 and 97.07%. All plans (HA, C-VMAT, and NC-VMAT) satisfied 100% of the prescription dose covering 95% of the PTV_{60} and PTV_{46} volume. In the maximum dose, the HA plan showed a higher D_2 dose in GTV (63.74, 63.38, and 63.26 Gy) and PTV_{60} (63.81, 63.50, and 63.36 Gy) than the C-VMAT and NC-VMAT. The maximum dose for all the plans was within 110% of the prescription dose (66 Gy).

Sparing of organs at risk. The HA plan demonstrated reduction to all the OARs (Table III). The isodose distributions of HA, C-VMAT, and NC-VMAT plans for one patient are illustrated in Figure 1. The HA plan spares the normal brain compared to the other two techniques. The mean normal brain dose of all patients for HA, C-VMAT, and NC-VMAT plans was 15.81, 19.02, and 17.62 Gy (Figure 2A). It decreased 16.88 and 10.27% in the HA plan compared to C-VMAT, and NC-VMAT plans. The V_{15Gy} for the normal brain was 34.13, 46.69, and 41.31% (Figure 2B). It decreased 12.56 and 7.18 % in the HA plan compared to C-VMAT, and NC-VMAT plans; the V_{30Gy} was 7.45, 18.42, and 13.6% (Figure 2C), it decreased 10.51 and 6.15 % in the HA plan compared to C-VMAT, and NC-VMAT plans; the V_{45Gy} was 2.60, 4.95, and 3.77% (Figure 2D), it decreased 2.35 and 1.17% in the HA plan compared to C-VMAT, and NC-VMAT plans; and the V_{60Gy} was 0.24, 0.27 and 0.34%, it decreased 0.1 and 0.03 % in the HA plan compared to C-VMAT, and NC-VMAT plans. The maximum brainstem dose was 47.93,

Table II. *Dosimetric parameters for targets.*

Target dose (Gy)	HA	C-VMAT	NC-VMAT	ANOVA	Post-hoc analysis	
					HA *vs.* C-VMAT	HA *vs.* NC-VMAT
	Mean (SEM)	Mean (SEM)	Mean (SEM)	*p*-Value	*p*-Value	*p*-Value
GTV coverage (%)	99.54 (0.20)	98.98 (0.35)	99.38 (0.24)	0.271	0.362	>0.999
D_2 (GTV)	63.74 (0.07)	63.38 (0.06)	63.26 (0.08)	<0.001*	10.002	<0.001*
D_{98} (GTV)	61.22 (0.02)	60.89 (0.04)	61.15 (0.03)	0.716	>0.999	>0.999
Mean dose (GTV)	62.65 (0.06)	62.50 (0.04)	62.49 (0.08)	0.141	0.321	0.216
CTV coverage (%)	99.97 (0.03)	99.96 (0.03)	99.99 (0.00)	0.585	>0.999	>0.999
PTV_{60} coverage (%)	97.27 (0.70)	96.34 (0.96)	97.07 (0.74)	0.697	>0.999	>0.999
D_2 (PTV_{60})	63.81 (0.07)	63.50 (0.06)	63.36 (0.08)	<0.001*	<0.001	<0.001*
D_{98} (PTV_{60})	59.33 (0.05)	58.79 (0.07)	59.32 (0.06)	0.766	>0.999	>0.999
Mean dose (PTV_{60})	62.40 (0.07)	62.28 (0.07)	62.32 (0.09)	0.555	0.866	>0.999
PTV_{46} coverage (%)	99.60 (0.12)	99.60 (0.11)	99.84 (0.03)	0.128	>0.999	0.230

C-VMAT: Coplanar volumetric arc therapy; NC-VMAT: non-coplanar volumetric arc therapy; HA: HyperArc; GTV: gross tumor volume; CTV: clinical target volume; $PTV_{46/60}$: planning treatment volume prescribed to 46/60 Gy. *Statistically significant, $p<0.05$.

Table III. *Dosimetric parameters for organs at risk (OARs).*

OAR dose (Gy)	HA	C-VMAT	NC-VMAT	ANOVA	Post-hoc analysis	
					HA *vs.* C-VMAT	HA *vs.* NC-VMAT
	Mean (SEM)	Mean (SEM)	Mean (SEM)	*p*-Value	*p*-Value	*p*-Value
Brainstem	47.93 (1.90)	48.29 (1.79)	48.76 (1.82)	0.950	>0.999	>0.999
Normal brain (mean)	15.81 (0.43)	19.02 (0.55)	17.62 (0.64)	<0.001*	<0.001*	0.067
Normal brain V_{15Gy}	34.13 (9.97)	46.69 (2.31)	41.31 (2.75)	<0.001*	<0.001*	0.101
Normal brain V_{30Gy}	7.45 (6.84)	18.42 (8.82)	13.60 (7.78)	<0.001*	<0.001*	0.016
Normal brain V_{45Gy}	2.60 (3.18)	4.95 (4.44)	3.77 (4.26)	0.103	0.101	0.847
Normal brain V_{60Gy}	0.24 (1.13)	0.34 (1.30)	0.27 (1.25)	0.957	>0.999	>0.999
Ipsilateral optic nerve	36.88 (3.44)	35.59 (3.90)	37.34 (3.63)	0.950	>0.999	>0.999
Contralateral optic nerve	19.07 (2.88)	19.68 (2.76)	20.74 (2.89)	0.947	>0.999	>0.999
Chiasma	40.62 (2.84)	40.68 (3.13)	42.60 (2.88)	0.878	>0.999	>0.999
Ipsilateral eye	19.96 (2.22)	25.98 (2.58)	23.14 (2.28)	0.216	0.245	>0.999
Contralateral eye	8.09 (1.76)	12.53 (1.80)	10.85 (1.77)	0.222	0.253	0.994
Ipsilateral lens	4.76 (0.36)	4.67 (0.45)	4.60 (0.27)	0.976	>0.999	>0.999
Contralateral lens	2.87 (0.26)	3.63 (0.41)	3.19 (0.32)	0.283	0.370	>0.999

C-VMAT: Coplanar volumetric arc therapy; NC-VMAT: non-coplanar volumetric arc therapy; HA: HyperArc. *Statistically significant, $p<0.05$.

48.29, and 48.76 Gy for the HA, C-VMAT, and NC-VMAT plans, respectively. The HA plan also reduced the dose to the contralateral optic structures, including the eye, lens, and optic nerve. The maximum contralateral optic nerve dose was 19.07, 19.68, and 20.74 Gy for the HA, C-VMAT, and NC-VMAT plans, respectively. The maximum dose to the contralateral eye was 8.09, 12.53, and 10.85 Gy, while that to the ipsilateral eye was 19.96, 25.98, and 23.14 Gy. For the contralateral lens, the maximum dose was 2.87, 3.63, and 3.19 Gy, respectively. Table III summarizes the results of the OARs for these three different plans.

Comparison of dosimetric index. Table IV and Figure 3 present a quantitative analysis of the dosimetric indexes.

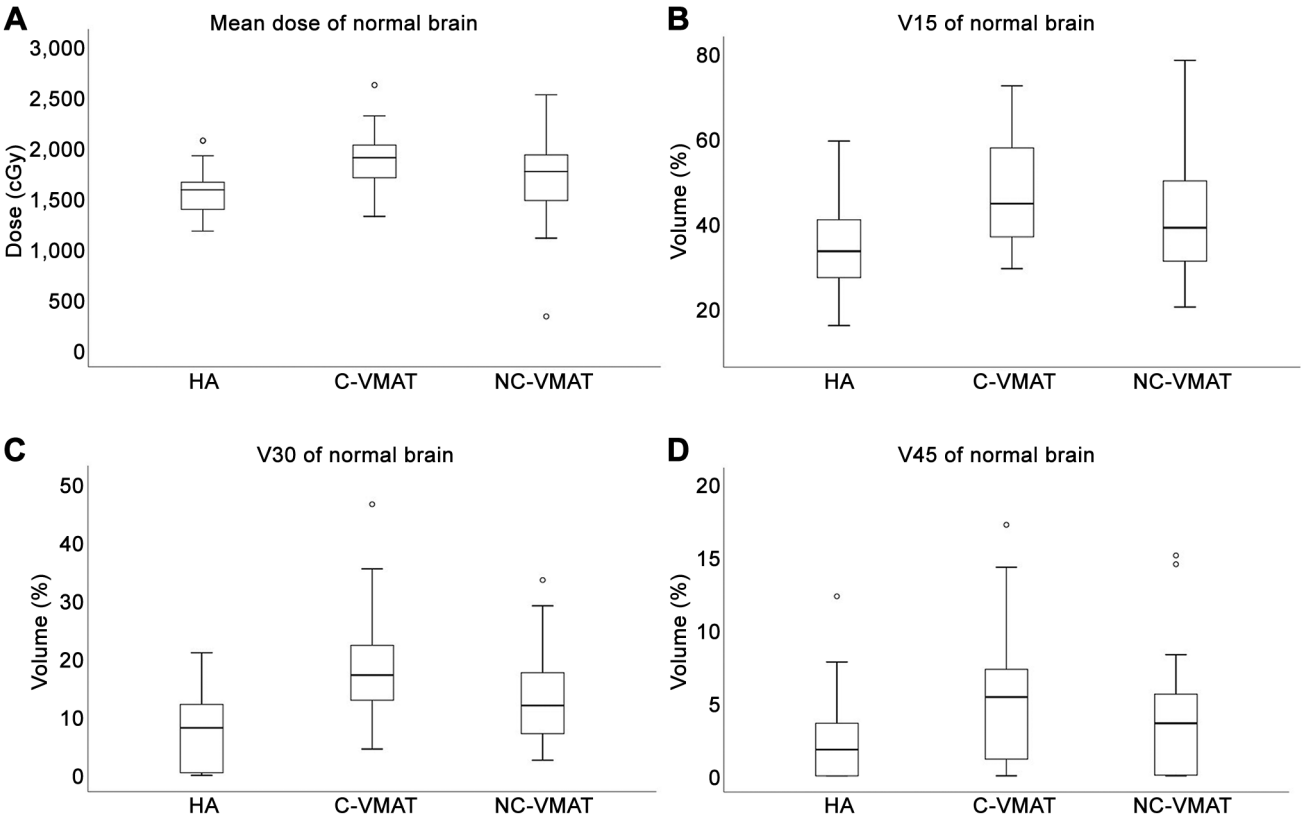

Figure 2. *Boxplots of dosimetric parameters of normal brain dose: mean dose, V_{15Gy}, V_{30Gy} and V_{45Gy} in the coplanar volumetric arc therapy (C-VMAT), non-coplanar VMAT (NC-VMAT), and HyperArc (HA) plans.*

The HA technique demonstrated a better CI in PTV_{60} and PTV_{46} compared to the other techniques. The CIs of PTV_{60} were 0.83, 0.79 and 0.76 for HA, C-VMAT and NC-VMAT, respectively (Figure 3A). $FPTV_{46}$, the CI values were 0.82, 0.70 and 0.70 for HA, C-VMAT and NC-VMAT, respectively. This indicates that the dose distribution of the HA plan exerted more conformity in all targets than the others. In the dose heterogeneity, the maximum dose of HA, C-VMAT and NC-VMAT plans was within 110% of the prescribed dose (66 Gy). The C-VMAT showed the lowest values in HI. The HI for PTV_{60} was 1.08, 1.08, and 1.07 for HA, C-VMAT, and NC-VMAT, respectively (Figure 3B).

In the dose fall-off comparison, HA shows the smaller gradient radius at PTV_{60} (1.61 cm *vs.* 2.03 cm *vs.* 1.90 cm) and PTV_{46} (0.94 cm *vs.* 1.27 cm *vs.* 1.14 cm) than C-VMAT and NC-VMAT (Figure 3C and D). HA plans had smaller intermediate dose spillage (3.42 *vs.* 4.45 *vs.* 4.11) of PTV_{60} than C-VMAT and NC-VMAT (Figure 3F) HA plans had smaller high dose spillage (0.17 *vs.* 0.34 *vs.* 0.33) and intermediate dose spillage (2.15 *vs.* 2.77 *vs.* 2.59) at PTV_{46} than C-VMAT and NC-VMAT (Figure 3E and G). This means that the dose distribution of the HA plan was tighter than those of the others, that indicated the dose to adjacent OAR were lower than those in C-VMAT and NC-VMAT plans. The HA plan required fewer MUs than others (p<0.001). The MUs were 956.30, 1261.14, and 1189.58 for HA, C-VMAT, and NC-VMAT, respectively.

Discussion

The standard treatment for GBM typically involves maximal surgical resection followed by RT combined with

Table IV. *Dosimetric parameters for dose distribution metrics.*

Dose distribution metrics	HA	C-VMAT	NC-VMAT	ANOVA	Post-hoc analysis	
					HA *vs.* C-VMAT	HA *vs.* NC-VMAT
	Mean (SEM)	Mean (SEM)	Mean (SEM)	*p*-Value	*p*-Value	*p*-Value
The maximal dose (Gy)	65.02 (0.11)	64.71 (0.12)	64.35 (0.11)	<0.001*	0.166	<0.001*
CI (PTV_{60})	0.83 (0.07)	0.76 (0.08)	0.79 (0.07)	0.095	0.111	0.366
CI (PTV_{46})	0.82 (0.04)	0.70 (0.05)	0.70 (0.05)	<0.001*	0.112	<0.001*
HI (PTV_{60})	1.08 (0.00)	1.08 (0.00)	1.07 (0.00)	<0.001*	0.112	<0.001*
High dose spillage (PTV_{60})	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)	>0.999	>0.999	>0.999
High dose spillage (PTV_{46})	0.17 (0.01)	0.34 (0.02)	0.33 (0.02)	<0.001*	<0.001*	<0.001*
Intermediate dose spillage (PTV_{60})	3.42 (0.17)	4.45 (0.25)	4.11 (0.03)	0.04	0.03	0.074
Intermediate dose spillage (PTV_{46})	2.15 (0.08)	2.77 (0.08)	2.59 (0.06)	<0.001*	<0.001*	<0.001*
Gradient radius (PTV_{60}, cm)	1.61 (0.05)	2.03 (0.07)	1.90 (0.07)	<0.001*	<0.001*	0.007
Gradient radius (PTV_{46}, cm)	0.94 (0.02)	1.27 (0.04)	1.14 (0.03)	<0.001*	<0.001*	<0.001*
Monitor unit	956.30 (22.83)	1261.14 (47.00)	1189.58 (31.33)	<0.001*	<0.001*	<0.001*

C-VMAT: Coplanar volumetric arc therapy; NC-VMAT: non-coplanar volumetric arc therapy; HA: HyperArc; CI: conformity index; HI: homogeneity index; $PTV_{46/60}$: planning treatment volume prescribed to 46/60 Gy. *Statistically significant, $p<0.05$.

temozolomide, a regimen associated with notable disfigurement and functional impairment (6, 28, 29). Furthermore, patients with GBM frequently experience unfavorable treatment outcomes, necessitating the utilization of advanced RT techniques to optimize treatment efficacy while mitigating the risk of radiation-induced side effects that can diminish the patient's quality of life (30, 31). The challenge of GBM RT is the tumor's irregular shape, large volume and adjacent OARs (31). Patients often experience fatigue and cognitive decline during and after RT due to the doses to central nervous system structures implicated in these symptoms (32). Gulliford *et al.* found that patients experienced acute fatigue of grade 2 or higher when significantly higher maximum and mean doses were administered to the brainstem and cerebellum compared to those without such symptoms (33). Our findings demonstrate that the HA plan could offer comparable tumor coverage, improved dose distribution, and better sparing of OARs than the previous techniques used for GBM RT (C-VMAT and NC-VMAT plans). The dose distribution of HA plans showed more conformity and tightened dose fall-off than the other plans.

Previous research has shown NC-VMAT to be non-inferior to C-VMAT, IMRT, and tomotherapy in treating gliomas (34, 35). However, the design of beam arrangement of manual NC-VMAT depends on planner skill and clinical experience. Besides, to prevent gantry-couch collisions, virtual dry run pre-treatment is necessary. During treatment, therapists need to enter the treatment room to rotate couch and gantry angles, and this prolongs patient in-room time and decrease treatment efficacy. Treatment efficacy remains a crucial quality metric in external beam RT procedures. Prolonged treatment times would increase the risk of patient intrafraction motion and the associated dosimetric uncertainties. In this study, we observed fewer MUs for the HA plans compared to the C-VMAT and NC-VMAT plans (956.3 *vs.* 1261.1 and 1,189.6, respectively). Although the HA's automated couch rotation during treatment eliminates the need for radiation therapists to enter the treatment room, the moving times between every couch angle needs 15 s. The

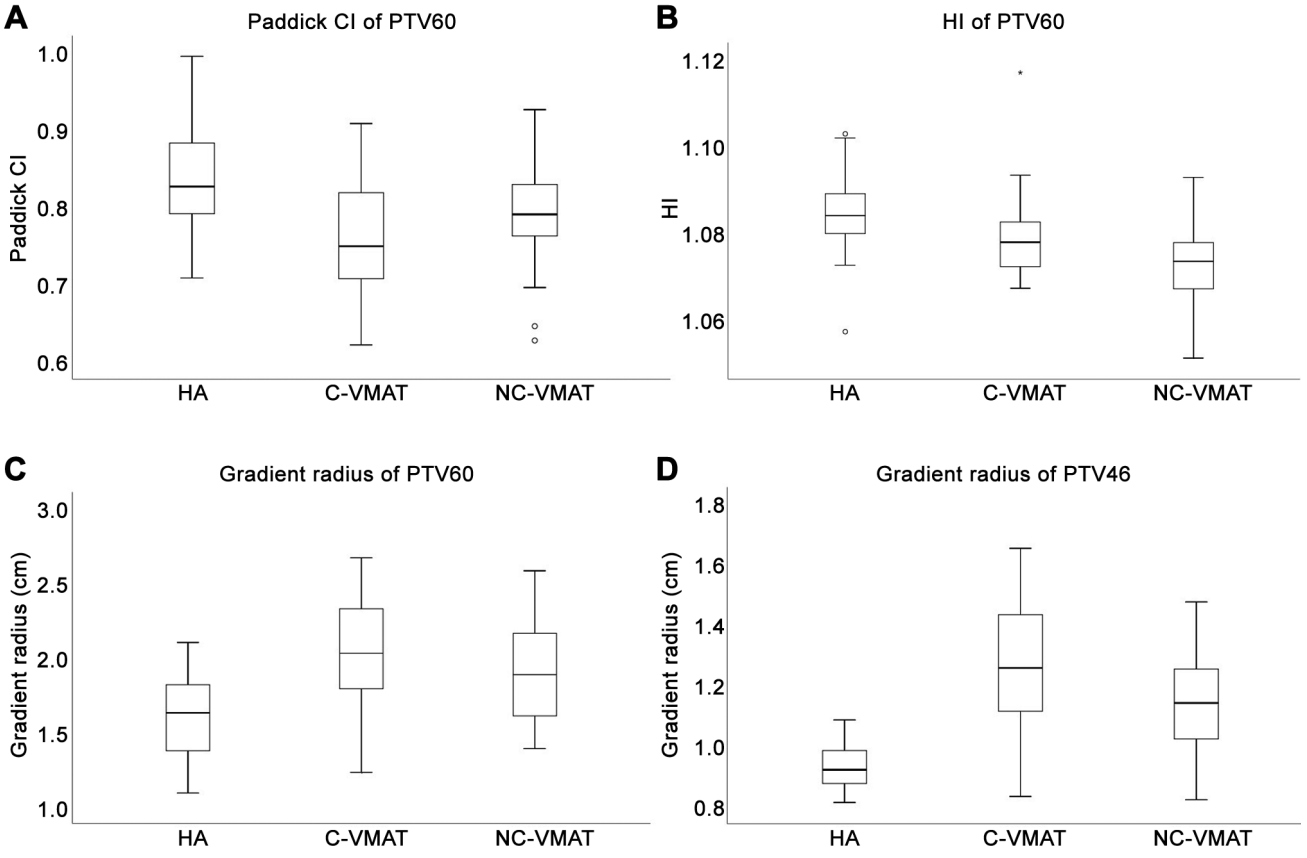

Figure 3. *Continued*

total room time in this study was 6 to 7 min and still within the acceptable in clinical range. Another point is that the use of nonplanar beam would increase some low dose areas than coplanar as show in the Figure 2. The critical organs in every beam path should be evaluated carefully.

Besides, the dose spread out in sequential radiotherapy (summation of initial and boost plans) is a potential problem. Our results show the HA had the better target conformity in all targets and tighter dose fall-off. The automatic HA plan modules could optimize collimator angles for each arc and employ jaw tracking to limit excessive radiation to critical structures (13, 15, 26). The application of SRS-NTO during optimization was a useful tool for reduction the dose spread out.

Recent research has shown that HA plans can provide even higher conformity in dose distribution, particularly in patients with brain metastases (10, 36). HA has also been applied to extracranial tumors, such as head and neck cancers (18, 37). In contrast to the previous research by Pan *et al.*, which utilized high-dose stereotactic radiotherapy to boost solitary GBM with 30 Gy in 5 fractions, comparing different machines (CyberKnife and conventional VMAT), this study focuses on comparing three linear accelerator -based treatment plans using conventional fractionated radiotherapy for GBM (20). Our results provide new evidence supporting the use of HA in treating GBM, which could form a new treatment approach. However, the clinical advantage of this dosimetric benefit is still under investigation. Future work is necessary to explore the association between dosimetric quality and clinical outcomes, including survival and toxicities.

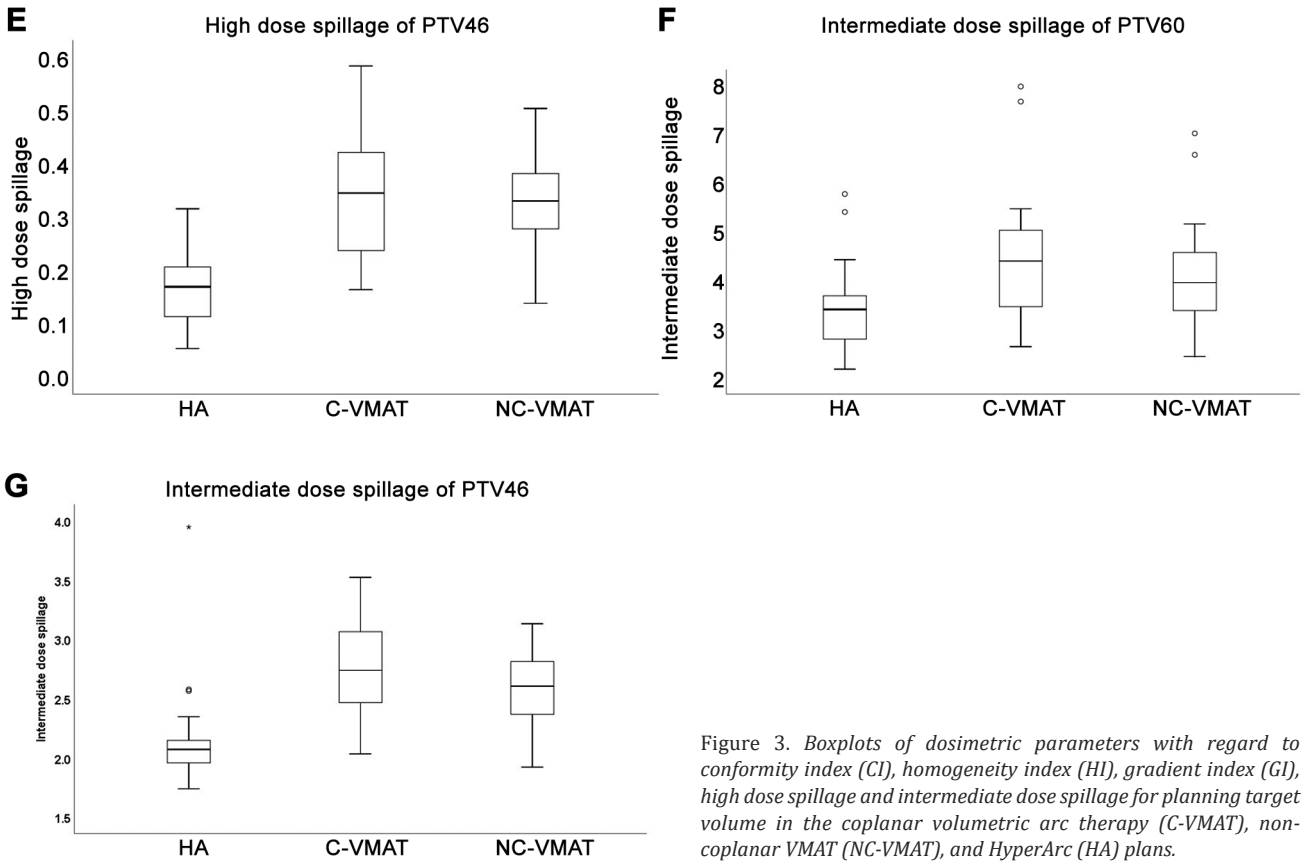

Figure 3. *Boxplots of dosimetric parameters with regard to conformity index (CI), homogeneity index (HI), gradient index (GI), high dose spillage and intermediate dose spillage for planning target volume in the coplanar volumetric arc therapy (C-VMAT), non-coplanar VMAT (NC-VMAT), and HyperArc (HA) plans.*

Study limitations. First, the small sample size of patients with GBM in the current study limited the analysis. Second, prior research has suggested that preserving neurocognitive function correlates with the brain receiving low doses of radiation. As this study was retrospective in design and no clinically significant outcomes were considered when using the HA technique, it remains uncertain to what extent toxicity may be mitigated with HA plans. Prospective studies are imperative to ascertain the actual outcomes concerning survival and side effects following treatment of patients with GBM. Nonetheless, the HA technique appears to hold substantial potential in mitigating neurocognitive decline due to its capacity to safeguard the brain or hippocampus. Despite these limitations, our findings offer evidence of HA's potential to expand the therapeutic window of RT in treating patients with GBM.

Conclusion

The novel HA technique provides comparable target coverage and better sparing of OARs, resulting in reduced radiation dose to the normal brain and optic apparatuses compared to C-VMAT and NC-VMAT plans. These findings support the idea that, alongside the advent of advanced cancer imaging tools and more potent systemic agents, HA could be employed to escalate tumor doses while mitigating toxicity, thereby potentially improving outcomes in patients with GBM.

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Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study design: Hong WJ; Ho HW; Lin HM; Lin T; Chow WH; Yang CC; Lin LC. Data analysis: Ho HW; Lin HM. Manuscript writing: Hong WJ; Ho HW; Yang CC. All Authors have read and agreed to the published version of the manuscript.

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