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Noncoplanar VMAT for Brain Metastases: A Plan Quality and Delivery Efficiency Comparison With Coplanar VMAT, IMRT, and CyberKnife

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Abstract

Purpose: To compare plan quality and delivery efficiency of noncoplanar volumetric modulated arc therapy with coplanar volumetric modulated arc therapy, intensity-modulated radiation therapy, and CyberKnife for multiple brain metastases. **Methods:** For 15 patients with multiple brain metastases, noncoplanar volumetric modulated arc therapy, coplanar volumetric modulated arc therapy, intensity-modulated radiation therapy, and CyberKnife plans with a prescription dose of 30 Gy in 3 fractions were generated. Noncoplanar volumetric modulated arc therapy and coplanar volumetric modulated arc therapy plans consisted of 4 noncoplanar arcs and 2 full coplanar arcs, respectively. Intensity-modulated radiation therapy plans consisted of 7 coplanar fields. CyberKnife plans used skull tracking to ensure accurate position. All plans were generated to cover 95% target volume with prescription dose. Gradient index, conformity index, normal brain tissue volume ($V_{3Gy} - V_{24Gy}$), monitor units, and beam on time were evaluated. **Results:** Gradient index was the lowest for CyberKnife (3.49 $\pm$ 0.65), followed by noncoplanar volumetric modulated arc therapy (4.21 $\pm$ 1.38), coplanar volumetric modulated arc therapy (4.87 $\pm$ 1.35), and intensity-modulated radiation therapy (5.36 $\pm$ 1.98). Conformity index was the largest for noncoplanar volumetric modulated arc therapy (0.87 $\pm$ 0.03), followed by coplanar volumetric modulated arc therapy (0.86 $\pm$ 0.04), CyberKnife (0.86 $\pm$ 0.07), and intensity-modulated radiation therapy (0.85 $\pm$ 0.05). Normal brain tissue volume at high-to-moderate dose spreads ($V_{24Gy} - V_{9Gy}$) was significantly reduced in noncoplanar volumetric modulated arc therapy over that of intensity-modulated radiation therapy and coplanar volumetric modulated arc therapy. Normal brain tissue volume for noncoplanar volumetric modulated arc therapy was comparable with noncoplanar volumetric modulated arc therapy at high-dose level ($V_{24Gy} - V_{15Gy}$) and larger than CyberKnife at moderate-to-low dose level ($V_{12Gy} - V_{3Gy}$). Monitor units was highest for CyberKnife (28 733.59 $\pm$ 7197.85), followed by intensity-modulated radiation therapy (4128.40 $\pm$ 1185.38), noncoplanar volumetric modulated arc therapy (3105.20 $\pm$ 371.23), and coplanar volumetric modulated arc therapy (2997.27 $\pm$ 446.84). Beam on time was longest for CyberKnife (30.25 $\pm$ 7.32 minutes), followed by intensity-modulated radiation therapy (2.95 $\pm$ 0.85 minutes), noncoplanar volumetric modulated arc therapy (2.61 $\pm$ 0.07 minutes), and coplanar volumetric modulated arc therapy (2.30 $\pm$ 0.23 minutes). **Conclusion:** For brain metastases far away from organs-at-risk, noncoplanar volumetric modulated arc therapy generated more rapid dose falloff and higher conformity compared to intensity-modulated radiation therapy and coplanar volumetric modulated arc therapy. Noncoplanar volumetric modulated arc therapy provided a comparable dose falloff with CyberKnife at high-dose level and a slower dose falloff than CyberKnife at moderate-to-low dose level. Noncoplanar volumetric modulated arc therapy plans had less monitor units and shorter beam on time than CyberKnife plans.

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Keywords
multiple brain metastases, noncoplanar VMAT, coplanar VMAT, IMRT, CyberKnife, dosimetry

Abbreviations
CI, conformity index; CK, CyberKnife; C-VMAT, coplanar volumetric modulated arc therapy; GI, gradient index; GK, Gamma Knife; GTV, gross tumor volume; HFSRT, hypofractionated stereotactic radiotherapy; NC-VMAT, noncoplanar volumetric modulated arc therapy; BEV, Beam's Eye View; BT, beam on time; IMRT, intensity-modulated radiation therapy; MIDCA, multi-isocenters dynamic conformal arcs; MLC, multileaf collimator; OARs, organs at risk; PTV, planning target volume; SIDCA, single-isocenter dynamic conformal arcs; SRS, stereotactic radiosurgery; VMAT, volumetric modulated arc therapy; WBRT, whole brain radiotherapy

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Introduction

Brain metastases have been reported in up to 40% of patients with systemic cancer,[1,2] and the incidence of brain metastases is increasing due to more sophisticated examination, such as brain magnetic resonance imaging screening and improved outcome of systemic therapy against primary cancers.

Most previous treatments include whole brain radiotherapy (WBRT), but more normal brain tissue was irradiated with WBRT resulting in more side effects. Therefore, it is crucial to spare normal brain tissue to decrease damages.[3,4] Recent studies have shown that adjuvant WBRT for patients with limited brain metastases increased cognitive decline without improving survival.[5,6] Brown *et al*[5] had compared patients (1-3 brain metastases) randomly treated with stereotactic radiosurgery (SRS) or SRS plus WBRT and found that SRS alone resulted in less cognitive deterioration at 3 months with no difference in overall survival. Yamamoto *et al*[7] found that SRS alone might be an alternative for multiple[5-10] brain metastases patients in a multi-institutional prospective observational study. However, the toxicity of SRS given in a single fraction increases risk of neurological morbidity from radionecrosis for large brain metastases.[8-11] Minniti *et al*[8] found a significant subset of patients who were treated with SRS developing neurological complications and suggested to consider hypofractionated stereotactic radiotherapy (HFSRT) to minimize the risk of symptomatic radionecrosis. It had been reported that HFSRT was an effective and safe way to treat large brain metastases.[12-16] Minniti *et al*[12] had found that HFSRT was effective to treat brain metastases, associated with better local control and reduced risk of radionecrosis as compared to SRS. Ogura *et al*[13] had found that HFSRT for brain metastases yielded high local control probabilities without increasing severe adverse events.

Currently, radiotherapy devices for brain metastases mainly include Gamma Knife (GK; Elekta AB, Stockholm, Sweden), CyberKnife (CK; Accuray, Sunnyvale, California), TomoTherapy (Accuray), and conventional C-arm linear accelerator. Treatment plan of multiple brain metastases is relatively complex because the targets are often surrounded by many critical and radiation-sensitive structures including brainstem, eyes, and lenses. Brain radionecrosis is also a very severe side reaction. A sharper dose falloff outside the targets is needed to protect organs at risk (OARs) better. The delivery of adequate radiation dose to the targets with lower dose to OARs is challenging for brain metastases, and each technique has its own advantages and disadvantages. The advantages of GK are quick dose falloff and better protection of normal brain tissue. CyberKnife combines a high-resolution image–guided tracking system to adjust the angle of beams during treatment to guarantee the accuracy of the treatment. The shortcoming of GK and CK is that the delivery time is much longer than conventional linear accelerator-based plan.[17-19] The dose falloff of intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) is not as quick as GK and CK.[20]

There are several studies investigating these techniques. But no systematic study was published comparing conventional C-arm linear accelerator and robotic radiosurgery for brain metastases. The aim of this study is to compare plan quality and delivery efficiency of noncoplanar VMAT (NC-VMAT) with coplanar VMAT (C-VMAT), IMRT, and CK plans for multiple brain metastases and to find the strengths and weaknesses of conventional C-arm linear accelerator and robotic radiosurgery.

Materials and Methods

This study was approved by Peking University Third Hospital Ethics Committee (approval no. M2019273), and written-informed consent requirement was waived. All the image data were deidentified by anonymization and analyzed retrospectively. Fifteen patients with 48 brain metastases, who were originally treated at our institution, were selected for this retrospective study.

All structures, including gross tumor volume (GTV) and OARs, were delineated by experienced radiation oncologists on Eclipse system (version 13.6; Varian Medical System, Palo Alto, California). The planning target volume (PTV) was generated by adding an isotropic margin of 2 mm to the GTV. Organs at risk included brainstem, eyes, lenses, optic nerves, optic chiasm, and pituitary.[21] The normal brain tissue was defined as healthy brain tissue minus PTV. The image sets

including all delineated structures were transferred via Digital Imaging and Communications in Medicine–radiotherapy to the CK Multiplan system (version 4.6; Accuray) for CK planning. The prescription dose (D_p) was 30 Gy in 3 fractions.[22] For OARs, the tolerance was set according to TG 101.[23] The treatment plans were generated to cover 95% volume of the PTV with D_p.

Linear accelerator plans were designed based on TrueBeam linear accelerator (Varian Medical System, Palo Alto, California) equipped with the Varian High Definition 120 multileaf collimator (MLC) with flattening filter free beams with 6-MV photon beams energy at a maximum dose rate of 1400 monitor unit (MU) per minute at Eclipse system. The type of MLC motion is sliding window. All doses were calculated by the means of an analytic anisotropic algorithm with the grid size of 1.25 mm. The single isocenter defined for all treatment plans was set at the center of mass of all brain metastases. Noncoplanar VMAT plans consisted of 4 noncoplanar arcs: 1 full arc with couch angle of 0° and 3 half arcs with couch angles of 45°, 315°, and 270°, respectively. Coplanar VMAT plans consisted of 2 coplanar arcs of 358° optimized simultaneously and to be delivered with opposite rotation (clock and counterclockwise). The first arc started at a gantry angle of 181° and stopped at 179°, and the second arc started at a gantry angle of 179° and stopped at 181°. The couch angle was set to 0° for both arcs. Intensity-modulated radiotherapy plans were optimized with 7 coplanar fields with the couch angle of 0°. The collimator angle for each technique was adjusted according to the location and size of the tumors in the Beam's Eye View (BEV).

CyberKnife combines a high-resolution image–guided tracking system to adjust the angle of beams during treatment to guarantee the accuracy of the treatment. CyberKnife plans were designed on Multiplan system via skull tracking and Ray-Tracing algorithm with 6-MV photon beams energy at a maximum dose rate of 950 MU per minute and were capable of noncoplanar, nonisocentric delivery. More than one iris collimators were used for each plan to reduce delivered MUs compared to using only one collimator. Collimators were chosen such that one collimator diameter was approximately equal to the central part of the largest lesion and the other was small enough to cover the tumor's smallest features. Several "autoshells" were created outside the target volume to constrain the conformity and the extent of the low-dose region.

Gradient index (GI)[24] described the steepness of the dose gradient from D_p to 50% of D_p ($GI = V_{50\%Dp}/V_p$, where $V_{50\%Dp}$ is 50% of the prescription isodose line volume and V_p is the prescription volume). Conformity index (CI)[24] was calculated to evaluate the degree of conformity of the dose distribution ($CI = (V_{tp})^2/(V_t \times V_p)$, where V_{tp} is the PTV volume within the prescription isodose surface, V_t is the PTV volume and V_p is the prescription volume). For normal brain tissue, volumes receiving a specific dose in the range of 3 to 24 Gy ($V_{3Gy} - V_{24Gy}$) were evaluated. In addition, delivery parameters were recorded including MUs and beam on time (BT).

To assess the difference among the plans, the Wilcoxon signed rank test was performed using the Statistical Package for Social Science, version 24.0, software (IBM, New York). A P value of $<.05$ was considered to indicate statistical significance.

Results

There were 15 (10 male and 5 female) patients in this study, and the median age of them was 67 years (range 36-81 years). The number of lesions ranged from 2 to 5 (2 lesions: 7, 3 lesions: 2, 4 lesions: 2, 5 lesions: 4). The median metastases volume was 6.66 cm^3 (range 1.49-38.64 cm^3). The distances between targets and the nearest OARs for all the patients were larger than 1 cm. All plans generated with 4 techniques were clinically acceptable, but differences were observed in the dosimetric parameters, MUs, and BT. Data were presented as mean values $\pm$ standard deviation.

Figure 1 presented the isodose distribution for a representative case for the 4 techniques under investigation. It can be observed that the CK and NC-VMAT plans provided a steeper dose gradient than IMRT and C-VMAT plans (V_{12Gy} of this example for CK, NC-VMAT, C-VMAT, and IMRT was 164.11, 230.73, 268.53, and 281.53 cm^3, respectively).

The dosimetric parameters and delivery parameters were shown in Table 1. The GI was the lowest for CK, followed by NC-VMAT, C-VMAT, and IMRT. The CI was the largest for NC-VMAT, followed by C-VMAT, CK, and IMRT. The MUs was the highest for CK, followed by IMRT, NC-VMAT, and C-VMAT. The BT was the longest for CK, followed by IMRT, NC-VMAT, and C-VMAT.

The absolute volume of the brain tissue receiving a specific dose was listed in Table 2 for 4 treatment plans. The mean absolute volume was lower in the NC-VMAT plans than IMRT and C-VMAT plans, and a significant difference was observed at the dose level ranges from 24 to 9 Gy ($V_{24Gy} - V_{9Gy}$). In contrast, a very low-dose volume ($V_{6Gy} - V_{3Gy}$) in NC-VMAT plans resulted in a somewhat larger dose spread than IMRT and C-VMAT plans. It can be observed that NC-VMAT plans provided a comparable dose volume with CK plans at the dose level ranges from 24 to 15 Gy ($V_{24Gy} - V_{15Gy}$). As dose decreased, the mean absolute volume was lower in the CK plans than NC-VMAT plans, and a significant difference was observed at the dose level ranges from 12 to 3 Gy ($V_{12Gy} - V_{3Gy}$).

The variations in GI and V_{12Gy} with different target volume, number of targets, and distance between targets and nearest OARs were plotted in Figure 2. The GI of CK and NC-VMAT were smaller than IMRT and C-VMAT. Gradient index decreased with the increase in target volume and increased with the increase in number of targets. With the distance between targets and nearest OARs increasing, GI changed little. The $V_{12\ Gy}$ of CK and NC-VMAT were smaller than IMRT and C-VMAT. $V_{12\ Gy}$ increased with the increase in target volume and number of targets. With the distance between targets and nearest OARs increasing, $V_{12\ Gy}$ changed little.

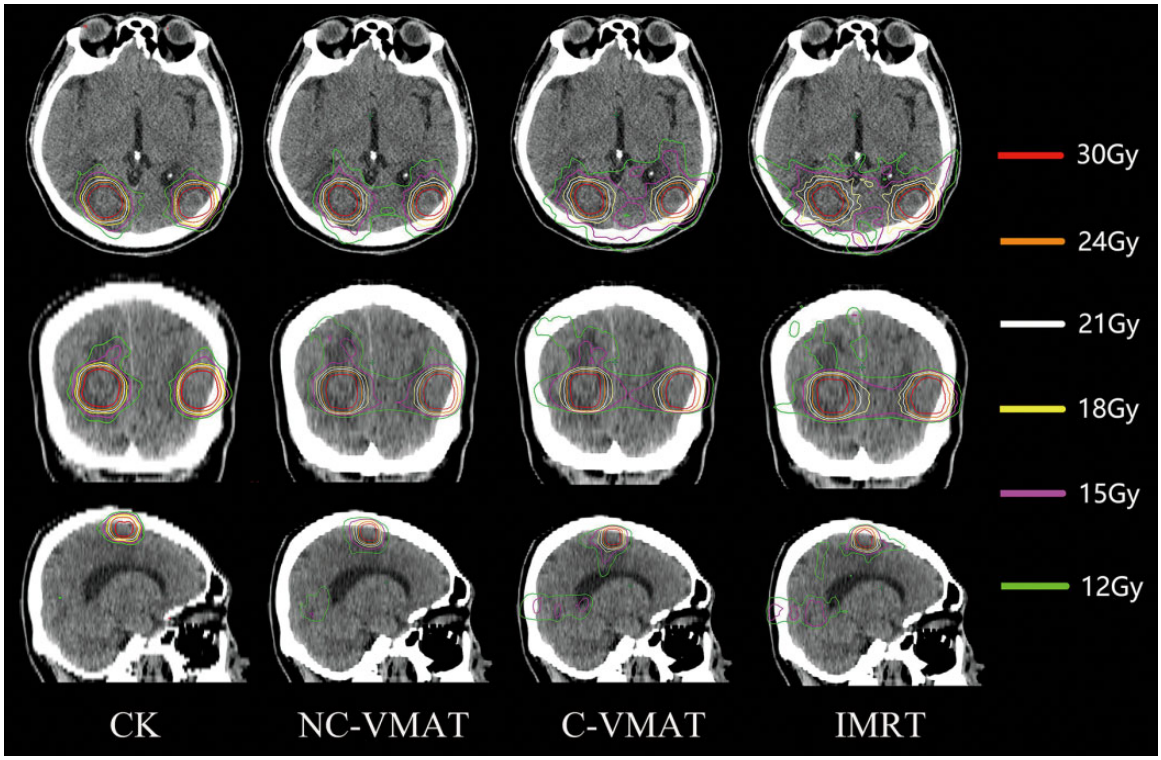

Figure 1. Dose distributions of CK, noncoplanar VMAT, coplanar VMAT, and intensity-modulated radiotherapy plans in the axial plane (upper), coronal plane (center), and sagittal plane (lower) for a typical patient. VMAT indicates volumetric modulated arc therapy and CK incicates CyberKnife.

Table 1. Evaluation Parameters of NC-VMAT, C-VMAT, IMRT, and CK Plans (Mean ± SD).[a]

Parameter	NC-VMAT	C-VMAT	*P*	IMRT	*P*	CK	*P*
GI	4.21 ± 1.38	4.87 ± 1.35	.001	5.36 ± 1.98	.001	3.49 ± 0.65	.015
CI	0.87 ± 0.03	0.86 ± 0.04	.008	0.85 ± 0.05	.002	0.86 ± 0.07	.281
MUs	3 105.20 ± 371.23	2 997.27 ± 446.84	.065	4 128.40 ± 1 185.38	.002	28 733.59 ± 7 197.85	.001
BT/min	2.61 ± 0.07	2.30 ± 0.23	.001	2.95 ± 0.85	.173	30.25 ± 7.32	.001

Abbreviations: BT, beam on time; CI, conformity index; CK, CyberKnife; C-VMAT, coplanar volumetric modulated arc therapy; GI, gradient index; IMRT, intensity-modulated radiation therapy; NC-VMAT, noncoplanar volumetric modulated arc therapy; MUs, monitor units; SD, standard deviation.
[a]Statistical significance was tested for each technology in comparison with NC-VAMT.

Table 2. Dosimetric Results for Normal Brain Tissue of NC-VMAT, C-VMAT, IMRT, and CK Plans (Mean ± SD).[a]

OARs		NC-VMAT	C-VMAT	*P*	IMRT	*P*	CK	*P*
Normal brain tissue volume, cm^3	V_{24Gy}	15.85 ± 7.05	17.40 ± 8.64	.010	20.45 ± 8.31	.001	17.98 ± 9.10	.100
	V_{21Gy}	25.97 ± 12.44	29.81 ± 15.73	.001	34.32 ± 15.55	.001	28.66 ± 14.70	.156
	V_{18Gy}	41.19 ± 21.45	49.39 ± 26.96	.001	55.57 ± 26.92	.001	41.63 ± 21.86	.820
	V_{15Gy}	68.19 ± 38.89	88.69 ± 53.71	.001	94.49 ± 48.74	.001	61.60 ± 33.02	.100
	V_{12Gy}	124.69 ± 79.48	165.98 ± 109.97	.001	168.56 ± 96.88	.001	94.97 ± 52.41	.015
	V_{9Gy}	236.12 ± 157.32	285.76 ± 177.29	.001	280.76 ± 172.16	.008	171.50 ± 104.34	.003
	V_{6Gy}	435.47 ± 276.56	467.69 ± 250.10	.088	424.23 ± 230.52	.955	324.49 ± 199.67	.004
	V_{3Gy}	793.03 ± 371.40	742.99 ± 302.19	.156	635.20 ± 274.93	.005	597.33 ± 293.26	.001

[a]Statistical significance was tested for each technology in comparison with NC-VAMT.
Abbreviations: CK, CyberKnife; C-VMAT, coplanar VMAT; IMRT, intensity-modulated radiation therapy; NC-VMAT, noncoplanar volumetric modulated arc therapy; OARs, organs at risk; SD, standard deviation.

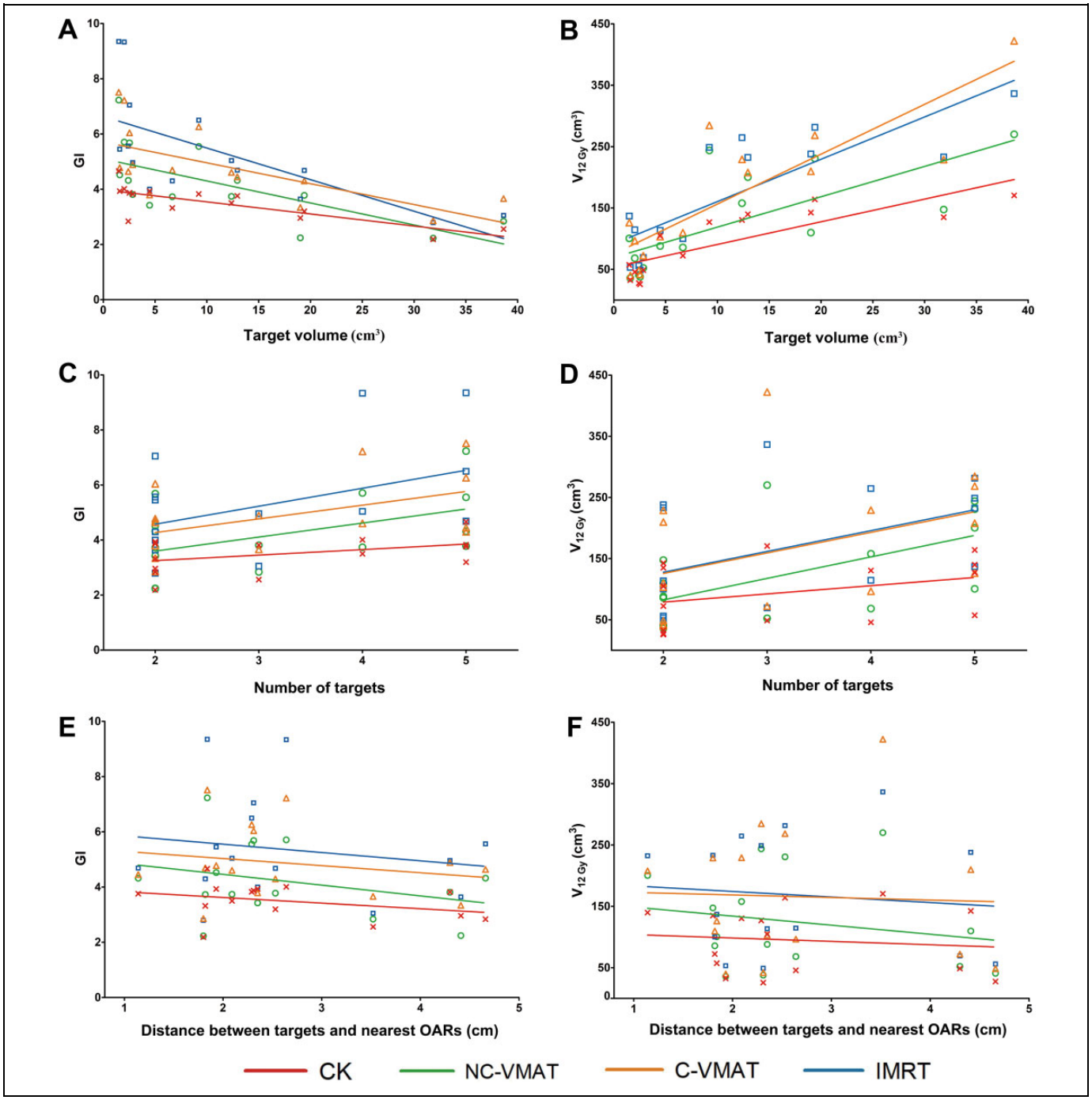

Figure 2. Comparison of gradient index (GI) and V_{12Gy} variation as a function of target volume, number of targets, and distance between targets and nearest organs at risk for 4 techniques. Dots are the actual value of GI or V_{12Gy}. Solid lines are fitting lines.

Discussion

There are many treatment techniques for multiple brain metastases, each with its own characteristics. This is the first study to compare plan quality and delivery efficiency of NC-VMAT, C-VMAT, IMRT, and CK for multiple brain metastases, with the aim to find the strengths and weaknesses of conventional C-arm linear accelerator and robotic radiosurgery. As the results indicated, dose falloff of NC-VMAT and CK plans was sharper than C-VMAT and IMRT plans. It was observed in GI and the normal brain tissue volume receiving a specific dose from 3 to 24 Gy, although some differences were not statistically significant. For cranial SRS/HFSRT, the V_{12Gy} was an important factor for the risk of radionecrosis.[25,10] In this study, the V_{12Gy} of CK was reduced by 31.3%, 74.8%, and 77.5% compared to NC-VMAT, C-VMAT, and IMRT plans, respectively. The V_{12Gy} of NC-VMAT was reduced by 33.1% and 35.2%

compared to C-VMAT and IMRT, respectively. CyberKnife and NC-VMAT plans were superior to C-VMAT and IMRT plans in terms of sparing of the normal brain tissue. Alongi *et al*[26] reported the clinical results of HyperArc (Varian Medical System, Palo Alto, California) and proved that the utilization of NC-VMAT treatment was safe and effective for brain metastases. Thomas *et al*[19] compared GK and multiarc VMAT plans. Multiarc VMAT plans were designed as 1-arc, 2-arc(noncoplanar), 4-arc(noncoplanar) with single isocenter. Compared to GK, multiarc VMAT had similar dose falloff. Ma *et al*[27] compared the plans of GK, CK, and Novalis. They found that dose of PTV and OARs was similar, but the dose of normal brain tissue was strongly apparatus-dependent. Compared to Novalis, GK and CK decreased the dose of normal brain tissue.

As shown in Figure 2, GI and V_{12Gy} varied with the target volume and number of targets. The volume of normal brain tissue that received high-dose irradiation around targets increased with the increase in target volume and number of targets. Although GI and V_{12Gy} varied with target volume and number of targets, the GI and V_{12Gy} of CK and NC-VMAT were both smaller than IMRT and C-VMAT. It demonstrated that noncoplanar irradiation could spare normal brain tissue better for the studied cases. In this study, the distance between targets and nearest OARs was larger than 1 cm. In this condition, the GI and V_{12Gy} of NC-VMAT and CK was smaller than C-VMAT and IMRT, which demonstrated the dose falloff advantage of noncoplanar irradiation. As for targets close to critical OARs, the dose falloff of noncoplanar technique was also sharper than coplanar technique.[28] Cao *et al*[28] compared the dosimetric characterization of different techniques for a patients with brain metastasis close to brainstem. The results showed that the GI of noncoplanar technique (GK, CK, and NC-VMAT) was smaller than coplanar technique (C-VMAT), which demonstrated the dose falloff advantage of noncoplanar irradiation. In this study, we found that normal brain tissue volume receiving a specific dose from 3 to 24 Gy was not always smaller for NC-VMAT than IMRT plans. The mean absolute volume was lower in the NC-VMAT plans than IMRT plans, and a significant difference was observed at the dose level ranges from 24-9 Gy ($V_{24Gy} - V_{9Gy}$). In contrast, a very low-dose volume ($V_{6Gy} - V_{3Gy}$) in NC-VMAT plans resulted in a somewhat larger dose spread than IMRT plans. This was because that the distance of opposite collimators was large enough to contain all targets that changing position with gantry rotating, and 2 or more targets share the same MLC leaf pair with gantry rotating, and the moving MLC would not block radiation to the normal tissue around targets in VMAT plans.[29] For IMRT plans, the distance of opposite collimators was set smallest according to the location and size of the tumors in the BEV, and MLC was arranged to block as much radiation as possible. Therefore, normal brain tissue volume was smaller for IMRT than NC-VMAT at low-dose level. Wu *et al*[30] reported the effect of using collimator optimization algorithm, which led to significant improvement in reducing the low dose to normal brain tissue, while retaining similar dose coverage to PTV.

The BT of CK was longer than linear accelerator plans. Slosarek *et al*[31] compared CK and VMAT and found that the delivery time of CK was longer than VMAT. This was because that the dose rate and size of collimator for CK was different from linear accelerator, and CK system consisted of a high-resolution image-guided tracking system that collected images during treatment and registered with previously generated projection images derived from the planning CT volume data set to reposition the linear accelerator automatically. The BT of VMAT was shorter than IMRT that was consistent with Yang's[32] and Zhao's[33] studies.

In this study, IMRT and VMAT plans were designed with single isocenter. Certainly, conventional C-arm linear accelerator can also be used to design multi-isocenters' plans. Clark *et al*[34] found that single-isocenter VMAT plans could be used to deliver conformity equivalent to that of multi-isocenters VMAT plans. Single-isocenter VMAT radiosurgery for multiple targets could be delivered extremely efficiently compared to multi-isocenters VMAT. Huang *et al*[35] had compared single-isocenter dynamic conformal arcs (SIDCA) with multi-isocenters dynamic conformal arcs (MIDCA) in radiosurgery treatment of multiple brain metastases. The plan quality of SIDCA was similar with MIDCA, and the delivery time was shorter than MIDCA. Patients only need to be placed once for single-isocenter plans and technicians do not have to re-enter treatment room during treatment process. It saves delivery time and improves clinical efficiency.

Conclusion

For brain metastases far away from OARs, NC-VMAT generated more rapid dose falloff and higher conformity compared to IMRT and C-VMAT. Noncoplanar VMAT provided a comparable dose falloff with CK at high dose level and a slower dose falloff than CK at moderate-to-low dose level. Noncoplanar VMAT plans had less MUs and shorter BT than CK plans.

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Declaration of Conflicting Interests

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