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Dosimetric comparison among dynamic conformal arc therapy, coplanar and non-coplanar volumetric modulated arc therapy for single brain metastasis

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ABSTRACT

In the delivery of stereotactic radiosurgery (SRS) by linear accelerator (LINAC), dynamic conformal arc therapy (DCAT) with non-coplanar beams is conventionally used. However, volumetric modulated arc therapy (VMAT) can improve target conformity, thereby decreasing the dose to organs at risk by inversed planning methods, but few studies have directly compared DCAT and VMAT with and without non-coplanar beams in patients with single brain metastasis. We therefore conducted a planning study to compare the dose distribution in DCAT, VMAT using only a coplanar arc (CoVMAT) and VMAT with non-coplanar arcs (NcVMAT) in the treatment of single brain metastasis. DCAT, CoVMAT and NcVMAT plans were created for 15 patients. The three modalities were compared in terms of target conformity, target coverage, the dose to normal brain tissue, monitor units (MUs) and beam-on time. Both conformity indices (RTOG-CI and IP-CI) as well as the $D_{98\%}$ of the gross target volume (GTV) were significantly better in the NcVMAT plans than in the DCAT plans. Comparisons of the doses to normal brain tissue revealed that the V_{20Gy}, V_{15Gy}, V_{12Gy}, V_{10Gy} and V_{5Gy} were significantly smaller in the NcVMAT plans than in the plans based on the other two modalities. The MUs of the DCAT and NcVMAT plans were larger than those of the CoVMAT plans, and the beam-on time was longer in the NcVMAT and CoVMAT plans than in the DCAT plans. Compared to the CoVMAT and DCAT plans, NcVMAT plans significantly improved target conformity and reduced the doses to normal brain tissue at V_{20Gy}, V_{15Gy}, V_{12Gy}, V_{10Gy} and V_{5Gy}.

Keywords: brain metastases; stereotactic radiosurgery (SRS); volumetric modulated arc therapy (VMAT); conformity index (CI)

INTRODUCTION

Among cancer patients, 20–40% will develop brain metastasis, which result in high rates of morbidity and mortality [1]. The most common primary site is the lung, followed by the breast and the gastrointestinal tract [2]. Among the treatment modalities used to treat brain metastasis are surgical resection, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), chemotherapy, molecular targeted therapy, immune checkpoint inhibitor and best supportive care. WBRT is the standard treatment for patients with multiple brain metastases and can achieve high intracranial progression-free survival, whereas SRS delivers high doses to the targets while sparing normal brain tissue [3].

With recent advances in systemic therapy, the prognosis of patients with brain metastasis has improved dramatically. Consequently, SRS is being increasingly adopted as an alternative to WBRT to achieve good long-term local control while reducing the risk of neurocognitive deficiency [4].

SRS is used in the treatment of tumors with a longest diameter <3 cm, as this upper limit results in local control and a lower risk of radiation necrosis, which increases with increasing tumor volume. Tumor size is an important predictor of local recurrence after SRS; Vogelbaum *et al.* reported that the rate of local recurrence and radionecrosis in brain metastases with a longest diameter >2.0 cm is higher compared to lesions ≤2.0 cm [5].

In the delivery of SRS using a linear accelerator (LINAC), dynamic conformal arc therapy (DCAT) with non-coplanar beams is the conventional strategy. However, with improvements in radiation therapy devices, volumetric modulated arc therapy (VMAT) has become the modality preferred by many institutions. With VMAT, the target conformity, target gradient and the doses to organs at risk can be adjusted using inversed planning methods [6].

In the clinical setting, VMAT is frequently delivered using coplanar arcs. Although, many institutions have adopted VMAT with only

coplanar arcs for the treatment of primary brain tumors, head and neck cancers and prostate cancers [7–9], there are few reports about superiority and inferiority to compare with VMAT using non-coplanar arcs. The addition of non-coplanar arcs may improve target conformity, but there were no planning studies to confirm this for single brain metastasis. This is the first study to compare DCAT, VMAT using only coplanar arcs (CoVMAT), and VMAT with non-coplanar arcs (NcVMAT) within the same treatment planning system (TPS) in patients with single brain metastasis.

Therefore, in this study we compared the target conformity, target coverage, normal brain tissue dose, monitor units (MUs) and beam-on time of these three modalities in the treatment of patients with single brain metastases with a longest diameter of 2–3 cm because it is the size of indication of SRS but the rate of local control and radionecrosis is inferior to the small lesion.

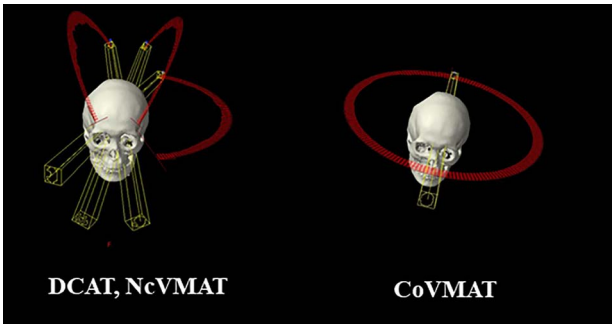

Fig. 1. Beam arrangement in a representative case in our study comparing DCAT, CoVMAT and NcVMAT.

MATERIAL AND METHODS

This study was conducted in accordance with the Declaration of Helsinki. The Institutional Ethical Review Board of our hospital approved the research (approval number R1048). Written consent was obtained from all patients enrolled in this study.

Patient population

The 15 patients enrolled in the study were treated for a single brain metastasis with the longest diameter of 2–3 cm. All patients were treated at our institution between April 2016 and October 2017.

Target and organ at risk delineation

Contouring and planning were performed using computed tomography (CT) images and Eclipse version 15.6 (Varian Medical Systems, Palo Alto, CA, USA). The CT images had a slice thickness of 1.25 mm and were acquired using a Light Speed RT scanner (GE Healthcare, Milwaukee, WI, USA). Contouring was delineated from the CT images and from magnetic resonance (MR) images. The gross target volume (GTV) was defined as the contrast-enhanced region on the MR images. The planning target volume (PTV) was defined as the GTV plus a 1-mm margin, to consider possible set-up errors and patient motion. The normal brain tissue was delineated as the whole brain minus the PTV. In VMAT planning, a ring contour was used to decrease the irradiated volume of normal brain tissue.

Treatment planning

DCAT, CoVMAT and NcVMAT plans were created for each of the 15 patients. A 6-megavolt beam, delivered by a TrueBeamSTx (Varian Medical Systems) device, was used in all patients. The dose was calculated using the AcurosXB dose calculation algorithm (ver. 15.6), and the calculation grid size was 1 mm. The prescribed dose for the PTV was 20 Gy in a single fraction, and each plan was normalized to $D_{99.5\%}$.

Dynamic conformal arc therapy plans

DCAT plans were based on one coplanar arc and two noncoplanar arcs (Fig. 1). The latter were placed at couch angles of 60° and 300° and rotated from 160° to 20° and from 200° to 300°, respectively. All collimator angles were set to 0°. In each plan, multi-leaf collimators (MLC) were modified to realize the $D_{2\%}$ of the PTV, which was set at ∼142% of the prescribed dose. Thus, the PTV was covered by the 70% isodose line of the 28.8 Gy delivered to the isocenter in a single fraction.

VMAT plans using coplanar arcs

Each CoVMAT plan was delivered using one coplanar arc that rotated clockwise from 181° to 179°; the collimator angle was set to 30°. The plan was optimized to satisfy the following criteria: a $D_{2\%}$ of the PTV of ∼142% of the prescribed dose, as described for the DCAT plan, and a mean dose to the PTV adjusted as in the DCAT plan. The dose to normal brain tissue was kept as low as possible by using a ring contour and the Normal Tissue Object function.

VMAT plans with non-coplanar arcs

NcVMAT plans were based on one coplanar arc and two non-coplanar arcs. The arc arrangement was also the same as in the DCAT plan and the collimator angle of coplanar arcs was set to 30°. The plans were optimized according to the criteria of the CoVMAT plan. The beam arrangements for the three plans are shown. (Fig. 1).

Evaluation of the treatment plans

The DCAT, CoVMAT and NcVMAT plans were compared based on the dose distribution using two conformity indices (CIs). The RTOG-CI was defined as:

$$V_{100\%}/V_{PTV}$$

where $V_{100\%}$ is the whole volume that received the prescription dose, and V_{PTV} is the PTV [10].

The second index was Paddick's conformity index (IP-CI), defined as [11]:

$$V_{PTV\,(100)}{}^2/\,(V_{100} \times V_{PTV})$$

where $V_{PTV\,(100)}$ is the volume of the PTV receiving the prescribed dose. The volume received by the normal brain tissue was estimated as V_{20Gy}, V_{15Gy}, V_{12Gy}, V_{10Gy} and V_{5Gy}, in which V_{XGy} was the normal brain tissue volume that received X Gy.

Table 1. Summary of the PTV indices

Index	DCAT	CoVMAT	NcVMAT (Mean ± SD)	P-value (ANOVA)	P-value (DCAT *vs* CoVMAT)	P-value (DCAT *vs* NcVMAT	P-value (CoVMAT *vs* NcVMAT)
RTOG-CI	0.73 ± 0.08	0.76 ± 0.09	0.82 ± 0.05	<0.05	0.09	<0.05	0.22
IP-CI	0.72 ± 0.07	0.78 ± 0.07	0.83 ± 0.04	<0.05	<0.05	<0.05	0.72
$D_{2\%}$ (Gy)	27.9 ± 0.7	27.8 ± 1.5	28.5 ± 1.4	0.23			
$D_{50\%}$ (Gy)	26.2 ± 0.6	25.9 ± 1.3	26.5 ± 0.9	0.29			
$D_{98\%}$ (Gy)	21. 0 ± 0.4	21.1 ± 0.5	21.2 ± 0.3	0.96			
D_{mean} (Gy)	25.7 ± 0.5	25.5 ± 1.2	25.9 ± 0.8	0.46			

PTV, planning target volume; SD, standard deviation; DCAT, dynamic conformal arc therapy; CoVMAT, coplanar volumetric modulated arc therapy; NcVMAT, non-coplanar volumetric-modulated arc therapy.
RTOG-CI CI is defined as $V_{100\%}/V_{PTV.}$; $V_{100\%}$ is defined as the whole volume receiving the prescription dose; V_{PTV} is defined as the PTV volume; Ian Paddick's conformity index (IP-CI) is defined by Paddick *et al.* as $V_{PTV\,(100)}{}^2 / (V_{100} \times V_{PTV})$; $V_{PTV\,(100)}$ is defined as the volume of the PTV receiving the prescribed dose according to Paddick *et al.*; $D_{2\%}$ is defined as the dose to 2% of the volume; Dmean is defined as the mean dose of the PTV.

Table 2. Summary of the GTV indices

Index	DCAT	CoVMAT	NcVMAT (Mean ± SD)	P-value (ANOVA)	P-value (DCAT *vs* CoVMAT)	P-value (DCAT *vs* NcVMAT	P-value (CoVMAT *vs* NcVMAT)
$D_{2\%}$ (Gy)	28.0 ± 0.7	27.3 ± 1.5	28.6 ± 1.3	0.18			
$D_{50\%}$ (Gy)	27.5 ± 1.0	26.7 ± 1.3	27.5 ± 1.1	0.051			
$D_{98\%}$ (Gy)	23.6 ± 0.3	23.7 ± 0.7	24.2 ± 0.5	<0.05	<0.05	<0.05	<0.05
D_{mean} (Gy)	26.6 ± 0.6	26.4 ± 1.3	27.2 ± 1.0	0.21			

GTV, gross target volume; SD, standard deviation; DCAT, dynamic conformal arc therapy; CoVMAT, coplanar volumetric modulated arc therapy; NcVMAT, non-coplanar volumetric-modulated arc therapy.
$D_{2\%}$ is defined as the dose to 2% of the volume; $D_{50\%}$ is defined as the dose to 50% of the volume; $D_{98\%}$ is defined as the dose to 98% of the volume; Dmean is defined as the mean dose of the GTV.

Statistical analysis

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitamasct/SaitamaHP.files/manual.html), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria, version 3.6.3). Specifically, EZR is a modified version of R commander version 2.6-2 and is used in bio-statistical evaluations [12].

Data from the three planning techniques (DCAT, CoVMAT and NcVMAT) were compared in a two-way analysis of variance (ANOVA) for the CIs and for the PTV and GTV ($D_{2\%}$, $D_{50\%}$, $D_{98\%}$ and D_{mean}) indices. Bonferroni post-hoc testing was also performed. A repeated-measures ANOVA was used to estimate normal brain tissue doses and was followed by Holm post-hoc testing because of the dependence of the data on the size of the PTV. A P-value <0.05 was considered to indicate statistical significance.

RESULTS

Target conformity and coverage

The median PTV was 6.4 cm^3 (range, 3.7–16.2). Table 1 summarizes the indices of the PTV. Both CIs (RTOG-CI and IP-CI) were significantly better for the NcVMAT plans than for the DCAT plans. Table 2 lists the GTV indices. The $D_{98\%}$ of the GTV of the NcVMAT plans was superior to that of the DCAT plans and CoVMAT plans.

Doses to the normal brain tissue

Table 3 summarizes the doses received by normal brain tissue. Significant differences identified in the entire cohort via a two-way ANOVA were further assessed using Holm post-hoc testing to compare pairs of modalities. The V_{20Gy}, V_{15Gy}, V_{12Gy}, V_{10Gy} and V_{5Gy} were significantly smaller in the NcVMAT plans than in the CoVMAT and DCAT plans. The V_{15Gy}, V_{12Gy}, V_{10Gy} and V_{5Gy} were significantly larger in the CoVMAT plans than in the DCAT and NcVMAT plans. Fig. 2 presents the axial and coronal planes of the dose distributions for the three modalities.

Monitor units and beam-on times

Table 4 summarizes the MUs and beam-on times. The MUs of the DCAT and NcVMAT plans were larger than those of the CoVMAT plans. The beam-on times were longer in the CoVMAT and NcVMAT plans than in the DCAT plans and CoVMAT plans.

DISCUSSION

This study compared the dose distributions of DCAT, CoVMAT and NcVMAT plans for patients with single brain metastasis. The doses to normal brain tissue were significantly lower in the NcVMAT plans than in the DCAT, CoVMAT plans. The CIs of the NcVMAT plans were better than those of the DCAT plans. To the best of our knowledge, this is the first report to directly compare DCAT, CoVMAT and NcVMAT plans in the treatment of single brain metastasis.

Brain metastases are often treated using DCAT with coplanar and non-coplanar arcs. DCAT delivered with non-coplanar arcs results in better CIs than those obtained with plans using only coplanar arcs.

Table 3. Summary of the irradiated volume of the normal brain tissue

Index	DCAT	CoVMAT	NcVMAT (Mean ± SD)	P-value (ANOVA)	P-value (DCAT *vs* CoVMAT)	P-value (DCAT *vs* NcVMAT)	P-value (CoVMAT vs NcVMAT)
V_{20Gy} (cm^3)	2.44 ± 1.78	2.48 ± 1.87	1.64 ± 1.13	<0.05	0.88	<0.05	<0.05
V_{15Gy} (cm^3)	7.22 ± 4.08	8.52 ± 4.89	5.95 ± 3.10	<0.05	<0.05	<0.05	<0.05
V_{12Gy} (cm^3)	11.6 ± 6.5	15.1 ± 8.2	9.4 ± 4.9	<0.05	<0.05	<0.05	<0.05
V_{10Gy} (cm^3)	16.8 ± 9.0	22.7 ± 12.0	13.9 ± 6.8	<0.05	<0.05	<0.05	<0.05
V_{5Gy} (cm^3)	49.2 ± 28.4	96.8 ± 55.4	42.9 ± 20.3	<0.05	<0.05	<0.05	<0.05

SD, standard deviation; DCAT, dynamic conformal arc therapy; CoVMAT, coplanar volumetric modulated arc therapy; NcVMAT, non-coplanar volumetric modulated arc therapy.
V_{xGy} is defined as the volume of the normal brain tissue receiving XGy.

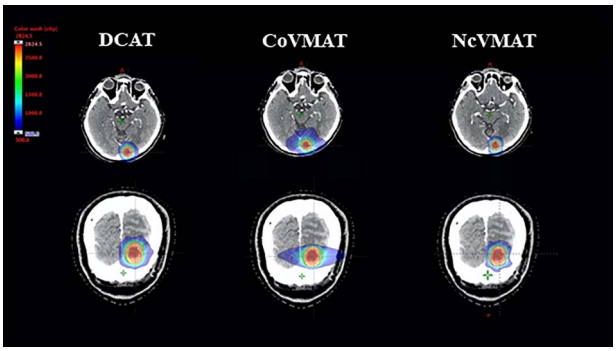

Fig. 2. Axial and coronal planes showing the dose distribution in a representative case. As shown by the color scale, the dose was >5 Gy.

The utility of NcVMAT plans in terms of target coverage and doses to organs at risk has been described for cancers such as nasopharyngeal cancer, craniopharyngiomas and frontal to temporal high-grade glioma [13–15]. However, no similar studies have investigated NcVMAT plans for the treatment of single brain metastasis.

To our knowledge, this is the first study to evaluate NcVMAT for single brain metastasis in SRS. A recent study reported that the $D_{98\%}$ of GTV was related to local control in multifraction stereotactic radiotherapy [16]. In our study, the $D_{98\%}$ of the GTV in the NcVMAT plans was superior to that of the DCAT and CoVMAT plans. The higher $D_{98\%}$ of GTV is likely to achieve good local control also in single-fraction SRS.

Factors related to the development of radionecrosis after SRS include treated volume and volume of the brain receiving a specific dose. Although the reported risk of radionecrosis after SRS is variable in reports depending on different modalities, type of lesion treated, the size of target and patient's selection, nevertheless V_{12Gy} may be used as the index to predict the risk of radionecrosis after SRS [17–19].

In the present results, we found that V_{12Gy} could be reduced with NcVMAT compared to the other two modalities. This finding suggests that the NcVMAT should be used for patients at risk of radionecrosis, such as those with a large brain metastasis. Therefore, it makes sense to improve dose distribution by VMAT planning with non-coplanar arcs.

In patients with brain metastases, high doses to the normal brain tissue should clearly be avoided to prevent radionecrosis, but this is also the case for low and intermediate doses. With advances in treatment, including chemotherapy, molecular target drugs and immune checkpoint inhibitors, the prognosis of patients with brain metastasis has improved. As a result, the use of SRS for brain metastases has been increasing. However, some patients will require re-treatment with a second course of SRS, such as when new intracranial brain metastases are identified on follow-up MR images. Given this possibility, it is important to reduce not only high doses but also low and intermediate doses to the normal brain tissue as much as possible. Our results revealed that NcVMAT plans can be used in the reduction of the V_{10Gy} and V_{5Gy}, thus lowering toxicity for patients with a good prognosis.

To our knowledge, the article reported by Molinier *et al.* is the only research paper directly comparing DCAT, CoVMAT and NcVMAT for multiple brain metastases [20]. Molinier *et al.* compared the dose distribution in intracranial lesions including primary brain tumors, single brain metastasis and multiple brain metastases. In this research, the TPS and calculation algorithm were different between DCAT and CoVMAT/NcVMAT. Also, the prescribed dose, the numbers of arcs and normalization isodose for each lesion were different.

In this study, on the other hand, the same TPS and calculation algorithm were applied to DCAT, CoVMAT and NcVMAT and the

Table 4. The MU rate and beam-on time in DCAT, CoVMAT and NcVMAT

Index	DCAT	CoVMAT	NcVMAT (Mean ± SD)	P-value (ANOVA)	P-value (DCAT *vs* CoVMAT)	P-value (DCAT *vs* NcVMAT)	P-value (CoVMAT *vs* NcVMAT)
MU	4326 ± 713	2297 ± 241	4095 ± 679	<0.05	<0.05	0.53	<0.05
Beam-on time	432 ± 71	488 ± 58	591 ± 72	<0.05	0.07	<0.05	<0.05

SD, standard deviation; DCAT, dynamic conformal arc therapy; CoVMAT, coplanar volumetric modulated arc therapy; NcVMAT, non-coplanar volumetric modulated arc therapy.

normalized isodose was unified. Because of the steep dose gradient in stereotactic radiotherapy, the prescribed dose and normalized isodose in the periphery are important for treatment planning. Therefore, in order to compare dose distributions, these factors need to be set identically among different modalities. Our article is the first report to compare dose distributions using the same TPS, calculation algorithm, prescribed dose and normalized isodose. Our study provides the most accurate assessment of the dose distribution compared to previously reported papers.

The limitations of this planning study must also be mentioned. First, the study design was retrospective, and could not reveal whether improved target CIs and reduced volume to normal brain tissue receiving doses of V_{10Gy} and V_{5Gy} led to practical benefits. Second, only brain metastases with a diameter of 2–3 cm were included. Whether NcVMAT can achieve a better dose distribution also for metastases outside this range is unclear but will be the subject of a future study. Third, while some institutions currently use VMAT with a single isocenter to treat multiple brain metastases, our study was limited to patients with a single brain metastasis. Further studies are needed to evaluate the applicability of our results in patients with multiple brain metastases. Fourth, higher CIs (i.e. closer to 1.0) or lower doses to normal brain tissue are considered to be prerequisites to achieve good brain metastasis control and to reduce brain necrosis, but this remains to be confirmed clinically. Finally, NcVMAT plans are more time-consuming than CoVMAT plans due to the need to transfer the couch angle. Additionally, VMAT plans require a quality assurance (QA) assessment, whereas this is not the case for VMAT in DCAT plans. A drawback to NcVMAT plans is that they require more MUs than CoVMAT plans and have a longer beam-on time than DCAT plans. Therefore, NcVMAT plans place a heavier burden on radiotherapists, medical physicists and other personnel involved in treatment. Also, a delay in starting treatment will risk changes in tumor size and location, a problem that is usually avoided by treatment planning and QA. The use of artificial intelligence and improved radiotherapy devices hold promise in shortening the delivery time and relieving the burden on personnel.

In conclusion, this study revealed that NcVMAT plans delivered a significantly lower dose to the normal brain tissue than either the DCAT or CoVMAT plans and achieved better CIs. This is the first study to directly compare DCAT, CoVMAT and NcVMAT plans for single brain metastasis. Our findings suggest that NcVMAT results in the achievement of a better dose distribution.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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