

Basic Original Report

Volumetric modulated Dynamic WaveArc therapy reduces the dose to the hippocampus in patients with pituitary adenomas and craniopharyngiomas



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Abstract

Purpose: Reducing the radiation dose to the hippocampus is important to preserve cognitive function in patients with brain tumors. The Vero4DRT system can realize a new irradiation technique, termed volumetric-modulated Dynamic WaveArc therapy (VMDWAT), which allows the safe use of sequential noncoplanar volumetric-modulated beams without couch rotation. Because VMDWAT appears to reduce the hippocampal dose in patients with pituitary adenomas and craniopharyngiomas, we performed a planning study to compare the dose distribution of volumetric-modulated arc therapy using only a coplanar arc (coVMAT) and VMDWAT.

Methods and materials: CoVMAT and VMDWAT plans were created for 30 patients with pituitary adenomas and craniopharyngiomas. The prescription dose was 52.2 Gy in 29 fractions, with 99% of each planning target volume covered by 90% of the prescribed dose. Optimization was performed for maximal reduction of the dose to the hippocampus. Treatment time was defined as the beam-on time.

Results: The mean equivalent dose in 2 Gy fractions to 40% of the volume of the bilateral hippocampus (EQD40%) for coVMAT/VMDWAT were 9.90/5.31 Gy, respectively ($P < .001$). The mean EQD40% in VMDWAT was less than 7.3 Gy, which is the threshold for predicting cognitive impairment. Although the volume of normal brain receiving 5 Gy (V5) was significantly larger in VMDWAT, compared with coVMAT, the normal brain volume receiving 10, 15, 20, 25, 30, 35, 40, 45, and 50 Gy (V10-50) was significantly smaller in VMDWAT. The conformity and homogeneity indices were significantly better in VMDWAT. The mean VMDWAT treatment time was longer compared with coVMAT (70.1 vs 67.1 seconds, respectively).

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Conflicts of interest: Kyoto University Hospital has a collaborative research agreement with Brainlab AG regarding the clinical evaluation of the treatment planning software for the Vero4DRT.

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Conclusions: Although VMDWAT increased brain V5 and the treatment time compared with coVMAT, it significantly reduced the dose to the hippocampus and brain V10 to V50 and improved target conformity and homogeneity. VMDWAT could be a promising treatment technique for pituitary adenomas and craniopharyngiomas.

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Introduction

The Vero4DRT system (Mitsubishi Heavy Industries, Ltd., Tokyo, Japan, and Brainlab, Feldkirchen, Germany) has a unique design in which the gantry is mounted within the O-ring structure (Fig 1).¹ Compared with conventional radiation therapy devices, the Vero4DRT can shorten the treatment time of stereotactic radiation therapy in patients with an intracranial tumor using rotations of the O-ring without the need to rotate the couch.² The gantry and O-ring can rotate simultaneously, allowing the use of sequential noncoplanar trajectories, which is a delivery method known as Dynamic WaveArc (DWA). The concept of DWA was developed as “unicursal irradiation”³ and the geometric verification and quality assurances were subsequently confirmed.^{4,5} DWA allows sequential noncoplanar beams to be safely and quickly used without rotating the couch. DWA can be realized with intensity modulated beams, and a new radiation technique that combines DWA with intensity modulation has been developed: volumetric-modulated Dynamic WaveArc therapy (VMDWAT).

In patients with an intracranial tumor, some studies have reported that noncoplanar beams could reduce the dose to organs at risk (OARs).⁶⁻⁸ Among the intracranial tumors, the prognoses of patients with pituitary adenomas and craniopharyngiomas tend to be good,^{9,10} and the long-term effects caused by radiation therapy must be considered. Neurocognitive dysfunction has been reported in patients

with pituitary adenomas and craniopharyngiomas who were treated with radiation therapy.^{10,11} Because the radiation dose to the hippocampus could be related to neurocognitive decline,¹²⁻¹⁴ and the bilateral hippocampus is located in close proximity to these tumors, it seems appropriate to reduce the dose to the hippocampus by the application of modern radiation techniques.

Our group conducted a planning study for craniopharyngiomas to compare the dose distribution of 3-dimensional dynamic conformal arc therapy (DCAT), volumetric modulated arc therapy using only coplanar arcs (coVMAT), and volumetric-modulated arc therapy using coplanar and noncoplanar arcs (ncVMAT).⁷ While ncVMAT significantly reduces the dose to the bilateral hippocampus without increasing the dose to normal brain tissue compared with DCAT and coVMAT, it also requires the couch to be rotated and the use of multiple arcs. As a result, the treatment time of ncVMAT must be longer than that of coVMAT.

Because VMDWAT uses sequential noncoplanar volumetric modulated beams without rotating the couch, it appears that VMDWAT can not only irradiate skull base tumors quickly and safely, but also reduce the dose to the hippocampus. To our knowledge, there are no reports in the literature regarding the use of VMDWAT for intracranial diseases; therefore, we conducted a planning study to compare coVMAT and VMDWAT in patients with pituitary adenomas and craniopharyngiomas.

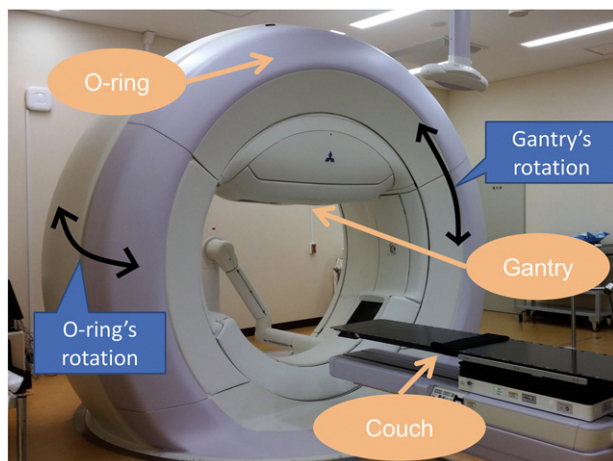


Figure 1 Unique design of the Vero4DRT system.

Methods and materials

This study was conducted in accordance with the Declaration of Helsinki, and our Institutional Ethical Review Board approved the research (approval number R0470-1). Written consent was obtained from all patients enrolled in this study.

Study population

A total of 30 patients were included in this study. All patients were diagnosed with pituitary adenomas or craniopharyngiomas and received fractionated stereotactic radiation therapy at our institution. Fifteen consecutive patients with pituitary adenomas were treated from April 2012 to February 2016, and 15 consecutive patients with

craniopharyngiomas were treated from November 2009 to April 2016.

Treatment planning

Patients were immobilized in thermoplastic masks, and planning computed tomography (CT) images 1.25-mm thick were acquired by a LightSpeed RT scanner (GE Healthcare, Milwaukee, WI). Pre- and postoperative magnetic resonance imaging scans were fused with the planning CT images.

Target and OAR delineation

Contouring and treatment planning were performed using acquired planning CT images and RayStation version 4.7 (RaySearch Laboratories, Stockholm, Sweden). In terms of the patients with pituitary adenomas, the clinical target volume (CTV) was defined as residual gross tumor. In patients with craniopharyngiomas, residual tumors were possibly present close to the surgical cavity, and a change in the size of the cystic lesion was often observed during radiation therapy¹⁵; therefore, the CTV of patients with craniopharyngiomas was defined to include any residual gross tumor and 5-mm thicknesses in any normal brain tissue attached to the tumor on preoperative magnetic resonance imaging scan. The planning target volume (PTV) was defined as the CTV plus a 2-mm margin to allow for setup and inter- and intrafractional localization errors.

The lenses, eyes, optic nerves, chiasm, brainstem, hippocampus, and normal brain were contoured as OARs. The hippocampus was delineated based on current concepts.¹⁶ The maximum doses to the brainstem, optic nerves/chiasm, eye, and lens were set at <59, 55, 45, and 10 Gy, respectively.

Treatment machine characterization

CoVMAT and VMDWAT plans were created for each of the 30 cases. Six-megavolt photon beams delivered by a Vero4DRT were used. The Collapsed Cone, version 3.1, calculation algorithm was used with a calculation grid size of 2.5 mm. The dose prescribed for the PTV was 52.2 Gy in 29 fractions, and all plans were normalized to ensure that V90 = 99% (ie, 99% of the PTV was covered by 90% of the prescribed dose).

Beam arrangement and optimization: CoVMAT planning

CoVMAT plans consisted of 1 coplanar arc that rotated clockwise from 182° to 178°. Optimization was performed until the final result met the following criteria: the maximum dose was set to be <107% of the prescribed dose, and the dose to the hippocampus was maximally reduced with keeping the dose coverage to the PTV. The higher priority objectives were satisfying the dose constraints to OARs (excluding the hippocampus and normal brain) and keeping the dose coverage to the PTV. Reducing the dose to the hippocampus was set as lower priority objective.

Beam arrangement and optimization: VMDWAT planning

VMDWAT plans were created using a symmetrical single noncoplanar arc trajectory (Fig 2). The arc trajectory was divided into 4 segments. The O-ring rotated from 0° to 40°, 40° to 0°, 0° to 320°, and 320° to 0° during the first, second, third, and fourth segments, respectively. The gantry rotated clockwise from 182° to 290°, 290° to 0°, 0° to 70°, and 70° to 178° in the first, second, third, and fourth segments, respectively. Optimization was performed to satisfy the same criteria as used in the coVMAT plans (see previous section).

Plan evaluation

To evaluate target conformity, 2 conformity indices (CIs) were calculated. One was the Radiation Therapy Oncology Group (RTOG)-CI, defined as $V(90)/VPTV$, where $V(90)$ is the volume enclosed by 90% of the prescription isodose surface, and VPTV is the PTV. The other index was Ian Paddick's conformity index, defined as $VPTV(90)^2/[V(90) \times VPTV]$,¹⁷ where VPTV(90) is the volume of the PTV receiving 90% of the prescribed dose.

Target homogeneity was evaluated using the International Commission on Radiation Units and Measurements homogeneity index (HI).¹⁸ The HI is defined as $(D2\% - D98\%)/D50\%$, where D2%, D98%, and D50% are the doses covering 2%, 98%, and 50% of the PTV, respectively. An HI value that is smaller and closer to 0 indicates a more homogenized dose distribution. The dose gradient was analyzed using Paddick's gradient index (P-GI).¹⁹ The P-GI was defined as $V(45)/V(90)$, where $V(45)$ is the volume enclosed by 45% of the prescription isodose surface. The doses to the bilateral, left, and right hippocampus were analyzed. We assessed the doses to 2%, 10%, 20%, 30%, 40%, 50%, 80%, and 98% of the hippocampus. The equivalent dose in 2-Gy fractions (assuming $\alpha/\beta = 2$) to X% of the hippocampus was defined

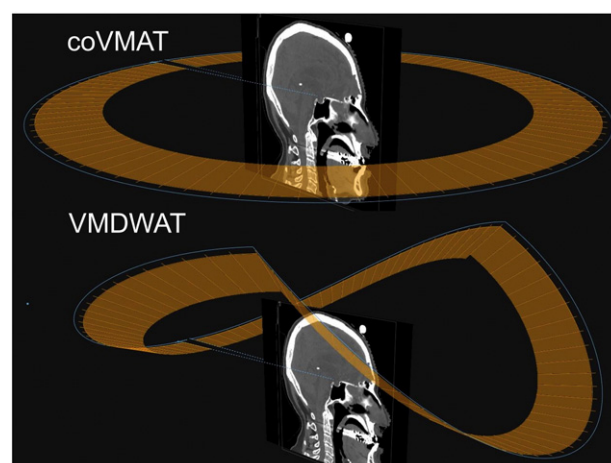


Figure 2 Arc arrangement of volumetric-modulated arc therapy (VMAT) using only coplanar arc (coVMAT) and volumetric-modulated Dynamic WaveArc therapy (VMDWAT) plans.

as EQDX%. The dose to the normal brain was assessed as follows: V5, V10, V15, V20, V25, V30, V35, V45, and V50 were defined as the volume of normal brain receiving 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 Gy, respectively. We also evaluated the doses to OARs, excluding the hippocampus and normal brain, using D2% and D50%.

We determined whether the created plans would work appropriately by transferring them to the Vero4DRT and checking the motion of the trajectory and multileaf collimators. The beam-on time was measured at the same time and was defined as the treatment time.

Statistical analysis

All statistical analyses were performed with the aid of EZR, version 1.32,²⁰ which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria; version 3.2.2). More precisely, EZR is a modified version of R commander version 2.2-3, facilitating biostatistical evaluations.

The coVMAT and VMDWAT plans were compared using the Wilcoxon signed-rank test and a paired *t* test. The Shapiro-Wilk test was used to determine whether the data had a normal distribution. A *P* value < .05 was considered to indicate statistical significance.

Results

The median PTV was 19.09 cm³ (range, 7.33-68.12 cm³). The mean values of the monitor unit (MU) of coVMAT and VMDWAT were 334.9 ± 40.6 and 360.7 ± 34.2, respectively, which were significantly different (*P* = .001). The mean treatment times were 67.1 ± 8.6 and 70.1 ± 0.4 seconds in the coVMAT and VMDWAT plans, respectively, which were significantly different (*P* = .045). All plans could be delivered without any problems. Coronal planes of the dose distribution in a representative case are shown in Fig 3.

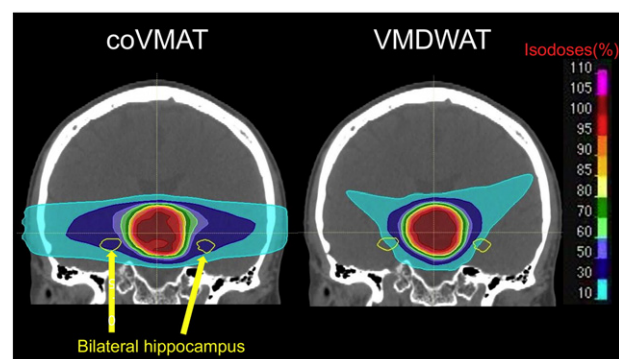


Figure 3 Coronal planes of the dose distribution in a representative case using volumetric-modulated arc therapy (VMAT) with coplanar arc (coVMAT) and volumetric-modulated Dynamic WaveArc therapy (VMDWAT).

Table 1 Indices for the planning target volume

Indices	coVMAT	VMDWAT (mean ± SD)	<i>P</i> value
D2% (Gy)	54.450 ± 0.511	53.974 ± 0.663	.001
D98% (Gy)	47.899 ± 0.169	47.847 ± 0.156	.183
D50% (Gy)	52.812 ± 0.667	52.392 ± 0.593	.007
RTOG-CI	1.257 ± 0.091	1.228 ± 0.087	<.001
IP-CI	0.783 ± 0.052	0.802 ± 0.050	<.001
P-GI	3.508 ± 0.240	3.219 ± 0.266	<.001
ICRU-HI	0.115 ± 0.407	0.109 ± 0.027	.011

coVMAT, volumetric-modulated arc therapy using only a coplanar arc; D2%, dose to 2% of the volume; D50%, dose to 50% of the volume; D98%, dose to 98% of the volume; ICRU-HI, homogeneity index defined by the International Commission on Radiation Units and Measurements¹⁸; IP-CI, Ian Paddick's conformity index¹⁷; P-GI, Ian Paddick's gradient index¹⁹; RTOG-CI, conformity index as defined by the Radiation Therapy Oncology Group; SD, standard deviation; VMDWAT, volumetric-modulated Dynamic WaveArc therapy.

Indices for the PTV

Table 1 summarizes the indices for the PTV. The mean conformity index (CI) as defined by the Radiation Therapy Oncology Group, Ian Paddick's conformity index, P-GI, and International Commission on Radiation Units and Measurements HI were significantly better in plans of VMDWAT than those of coVMAT.

Indices for the hippocampus

Table 2 summarizes the doses to the bilateral hippocampus. VMDWAT significantly reduced the mean EQD2%, EQD10%, EQD20%, EQD30%, EQD40%, EQD50%, EQD80%, and EQD98% of the bilateral, left, and right hippocampus compared with those of the coVMAT plans. The mean values of EQD40% to the bilateral hippocampus were 9.90 Gy and 5.31 Gy for coVMAT and VMDWAT, respectively.

Table 2 Doses to the bilateral hippocampus

Dose (Gy)	coVMAT	VMDWAT (mean dose ± SD)	<i>P</i> value
EQD2%	25.17 ± 11.34	22.46 ± 12.76	<.001
EQD10%	19.13 ± 10.45	15.04 ± 11.68	<.001
EQD20%	15.47 ± 9.67	10.63 ± 9.98	<.001
EQD30%	12.34 ± 8.05	7.43 ± 8.05	<.001
EQD40%	9.90 ± 6.13	5.31 ± 4.91	<.001
EQD50%	8.64 ± 5.13	4.57 ± 4.06	<.001
EQD80%	6.48 ± 3.70	3.27 ± 2.68	<.001
EQD98%	4.17 ± 2.62	2.24 ± 1.86	<.001

coVMAT, volumetric-modulated arc therapy using only a coplanar arc; EQDX%, equivalent dose in 2-Gy fractions (assuming $\alpha/\beta = 2$) to X% of the volume; SD, standard deviation; VMDWAT, volumetric-modulated Dynamic WaveArc therapy.

Table 3 Irradiated volume of normal brain

Volume (cm ³)	coVMAT	VMDWAT (mean ± SD)	P value
V5	458.95 ± 137.05	529.93 ± 177.31	<.001
V10	271.36 ± 132.34	250.33 ± 140.30	.001
V15	154.24 ± 87.29	121.78 ± 74.73	<.001
V20	83.92 ± 55.96	71.04 ± 43.85	<.001
V25	53.51 ± 35.57	45.40 ± 28.50	<.001
V30	33.61 ± 22.29	29.53 ± 19.95	<.001
V35	21.48 ± 14.12	20.21 ± 13.20	.003
V40	13.30 ± 8.76	12.77 ± 8.52	.014
V45	6.90 ± 4.95	6.46 ± 4.88	<.001
V50	1.39 ± 2.03	1.07 ± 1.66	<.001

coVMAT, volumetric-modulated arc therapy using only a coplanar arc; SD, standard deviation; VMDWAT, volumetric-modulated Dynamic WaveArc therapy; VX, the volume of normal brain receiving X Gy.

Indices for the normal brain and other OARs

Table 3 summarizes the irradiated volume of normal brain. Although the brain V5 of VMDWAT was significantly increased than that of coVMAT, VMDWAT significantly decreased the normal brain volume receiving 10, 15, 20, 25, 30, 35, 40, 45, and 50 Gy (V10-V50) compared with coVMAT.

The D2% of the left optic nerve and left eye in VMDWAT was significantly lower compared with that in coVMAT. There was no significant difference between 2 modalities in the D2% of chiasm, right optic nerve, right eye, both lens, and brainstem. Doses to OARs are summarized in Table 4.

Discussion

We conducted a planning study to compare the dose distribution between coVMAT and VMDWAT in patients with pituitary adenomas and craniopharyngiomas. We found that the dose to the hippocampus was significantly reduced in VMDWAT compared with coVMAT and that the mean EQD40% to the bilateral hippocampus in VMDWAT was lower than 7.3 Gy, which is the threshold for predicting cognitive deficit.¹² The target conformity and homogeneity were also better in VMDWAT compared with coVMAT.

VMDWAT as realized by the Vero4DRT can irradiate sequential noncoplanar volumetric-modulated beams safely and quickly. Dosimetric comparison between coVMAT and VMDWAT in extracranial regions was reported, and VMDWAT allowed an improvement in dose shaping within a similar treatment time.²¹ To our knowledge, this is the first study to perform dosimetric assessment of VMDWAT for intracranial disease. VMDWAT could quickly irradiate sequential noncoplanar volumetric modulated beams so that the intrafractional error could be small. In VMDWAT, there is no requirement to rotate the couch during treatment;

Table 4 Doses to organs at risk (hippocampus and normal brain excluded)

Structure/index (Gy)	coVMAT	VMDWAT (mean dose ± SD)	P value
Right optic nerve			
D2%	45.36 ± 9.42	45.60 ± 8.67	.880
D50%	18.78 ± 6.00	16.66 ± 7.01	.004
Left optic nerve			
D2%	47.00 ± 8.70	46.07 ± 9.59	.003
D50%	19.53 ± 6.11	17.96 ± 6.77	.019
Chiasm			
D2%	53.07 ± 2.83	52.93 ± 2.43	.387
D50%	50.33 ± 6.54	50.03 ± 6.69	.082
Right eye			
D2%	12.32 ± 2.37	11.94 ± 2.05	.336
D50%	8.49 ± 1.69	8.07 ± 1.39	.146
Left eye			
D2%	13.67 ± 2.88	12.62 ± 2.97	.008
D50%	9.21 ± 2.29	8.44 ± 1.97	.004
Right lens			
D2%	8.03 ± 1.32	8.38 ± 0.95	.269
D50%	7.04 ± 1.15	7.27 ± 1.11	.446
Left lens			
D2%	8.34 ± 1.28	8.17 ± 1.15	.182
D50%	7.16 ± 1.54	6.99 ± 1.21	.223
Brainstem			
D2%	44.13 ± 8.36	42.95 ± 9.05	.262
D50%	19.03 ± 7.33	19.47 ± 7.15	.428

coVMAT, volumetric-modulated arc therapy using only a coplanar arc; D2%, dose to 2% of the volume; D50%, dose to 50% of the volume; SD, standard deviation; VMDWAT, volumetric-modulated Dynamic WaveArc therapy.

therefore, the risk of causing nausea and patient rotation could be reduced.

Irradiation of the hippocampus could cause cognitive dysfunction and it would therefore seem sensible to reduce the dose to the hippocampus. Irradiation to the temporal lobes could increase the risk of cognitive dysfunction, and among temporal lobes the hippocampus appears to play an important role in memory functioning in irradiated patients.²² There have been some recent clinical trials aimed at sparing the hippocampus to preserve cognitive function in patients with brain tumors.^{13,14} With regard to patients with benign brain tumors and low-grade gliomas, a mean EQD40% >7.3 Gy was reported to predict cognitive decline.¹² We used VMDWAT for patients with pituitary adenomas and craniopharyngiomas; this technique was able not only to achieve better target conformity and homogeneity, but also to reduce the dose to the hippocampus compared with coVMAT. VMDWAT can also reduce moderate and high doses to the normal brain compared with coVMAT. VMDWAT could be the most appropriate treatment modality for patients with pituitary adenomas and craniopharyngiomas.

This study has some limitations. First, it was a planning study to evaluate the dose distribution of coVMAT and VMDWAT, and it is unclear whether dosimetric superiority actually leads to the preservation of neurocognitive function. We plan to conduct a prospective clinical trial to assess the feasibility of VMDWAT for patients with skull-based tumors and evaluate the clinical outcome. Second, there are factors other than the dose to the hippocampus that are related to neurocognitive dysfunction; these factors include surgery, the tumor itself, and hormonal abnormalities.²³ Third, VMDWAT increased brain V5 instead of decreasing brain V10 through V50. Because VMDWAT uses sequential noncoplanar beams, the path length of the beams from the skull to the isocenter tends to become longer compared with coVMAT, and the volume of normal brain with a low dose could be larger as a result. The effect of the increase in brain V5 is unknown and it is more important to reduce the dose to the hippocampus and the volume of normal brain receiving a moderate or high dose. In light of this, VMDWAT could be a promising technique for patients with pituitary adenomas and craniopharyngiomas.

Conclusions

VMDWAT significantly reduced the dose to the hippocampus, and the EQD40% was 5.31 Gy, which was lower than the threshold for predicting cognitive decline.¹² Target conformity and homogeneity were also significantly better in VMDWAT compared with coVMAT. Although brain V5 was increased in VMDWAT, brain V10 to V50 was also significantly decreased in VMDWAT. The treatment time in VMDWAT was found to be only 70 seconds. This is the first report on the use of VMDWAT for intracranial diseases, and it suggests that VMDWAT could be a promising treatment modality for pituitary adenomas and craniopharyngiomas.

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