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Assessment of multi-criteria optimization (MCO) for volumetric modulated arc therapy (VMAT) in hippocampal avoidance whole brain radiation therapy (HA-WBRT)

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Abstract

This study compared the dosimetric performance of (a) volumetric modulated arc therapy (VMAT) with standard optimization (STD) and (b) multi-criteria optimization (MCO) to (c) intensity modulated radiation therapy (IMRT) with MCO for hippocampal avoidance whole brain radiation therapy (HA-WBRT) in RayStation treatment planning system (TPS). Ten HA-WBRT patients previously treated with MCO-IMRT or MCO-VMAT on an Elekta Infinity accelerator with Agility multileaf collimators (5-mm leaves) were re-planned for the other two modalities. All patients received 30 Gy in 15 fractions to the planning target volume (PTV), namely, PTV30 expanded with a 2-mm margin from the whole brain excluding hippocampus with margin. The patients all had metastatic lesions (up to 12) of variable sizes and proximity to the hippocampus, treated with an additional 7.5 Gy from a simultaneous integrated boost (SIB) to PTV37.5. The IMRT plans used eight to eleven non-coplanar fields, whereas the VMAT plans used two coplanar full arcs and a vertex half arc. The averaged target coverage, dose to organs-at-risk (OARs) and monitor unit provided by the three modalities were compared, and a Wilcoxon signed-rank test was performed. MCO-VMAT provided statistically significant reduction of D100 of hippocampus compared to STD-VMAT, and Dmax of cochleas compared to MCO-IMRT. With statistical significance, MCO-VMAT improved V30 of PTV30 by 14.2% and 4.8%, respectively, compared to MCO-IMRT and STD-VMAT. It also raised D95 of PTV37.5 by 0.4 Gy compared to both MCO-IMRT and STD-VMAT. Improved plan quality parameters such as a decrease in overall plan Dmax and total monitor units (MU) were also observed for MCO-VMAT. MCO-VMAT is found to be the optimal modality for HA-WBRT in terms of PTV coverage, OAR sparing and delivery efficiency, compared to MCO-IMRT or STD-VMAT.

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KEY WORDS
dosimetric comparison, HA-WBRT, MCO, treatment planning, VMAT

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1 | INTRODUCTION

Brain metastases are an important source of morbidity for cancer patients. Whole brain radiation therapy (WBRT) is effective, but results in significant neurocognitive side effects for many patients, especially in terms of verbal memory. As survival for patients with metastatic brain disease increases,[1,2] approaches to spare neurocognition have become an intense area of study. Focal radiation with stereotactic radiosurgery (SRS) is one approach that results in less neurocognitive impairment,[3] but is not an option for many patients with more diffuse metastatic disease. One alternative that has gained popularity in the last several years has been hippocampal avoidance whole brain radiation therapy (HA-WBRT), which uses advanced radiation techniques to reduce the dose to the hippocampus, an area important for memory formation and neurogenesis.[4] The RTOG 0933 phase II study showed evidence of improvements in quality of life and memory preservation compared to historical WBRT controls.[4] Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R) revealed a 30% mean relative decline in WBRT without hippocampal avoidance (baseline 4 months) versus 7% utilizing HA-WBRT along with no decline in Quality of Life scores (QOL).[4]

Intensity modulated radiation therapy (IMRT) has been used as a practical delivery method for HA-WBRT based on RTOG 0933 guidelines.[5] Dose painting to metastatic lesions, although not required by the RTOG protocol, has also been examined.[6] Despite these efforts, recent survey results from Slade et al.[7] indicated 56% of radiation oncologists (n = 196) would not consider (IMRT) for HA-WBRT; among several factors was the complexity of the treatment planning process which requires substantial training. More recently, volumetric modulated arc therapy (VMAT) has also been examined for HA-WBRT.[8] VMAT showed superior dosimetric performance to IMRT,[9,10] and can practically deliver dose painting in form of simultaneous integrated boost (SIB)[11] to multiple brain metastases,[12,13] along with HA-WBRT.[14,15]

Dosimetric quality and efficiency for IMRT and VMAT were further promoted by a recent advancement in inverse planning technology: multi-criteria optimization (MCO).[16–21] MCO generates a Pareto surface containing a spectrum of optimal plans, with every point on the surface representing an optimal solution with different trade-off objectives.[16] A user is able to navigate combinations in real-time based on specified trade-off objectives along with planning constraints.[16] Numerous studies have confirmed that MCO improved plan quality over conventional inverse planning methods.[17–21] In addition, MCO also reduced planning time and allowed less-experienced treatment planners to efficiently produce high-quality IMRT plans for complex targets in the close vicinity of numerous organs-at-risk (OARs), such as tumors in the head and neck region.[20]

The study aimed to compare three treatment planning methods – IMRT with MCO (MCO-IMRT), VMAT with standard optimization (STD-VMAT) and VMAT with MCO (MCO-VMAT), for HA-WBRT on complex targets with a variety of conditions (0–12 metastatic lesions with variable lesion sizes and different proximity to the hippocampus). The effectiveness of using SIB to deliver the extra dose to the metastatic lesions was also assessed for all three methods.

2 | MATERIALS AND METHODS

2.A | Patient selection

Ten patients previously treated with HA-WBRT using MCO-IMRT (eight patients in RayStation v4.0) or MCO-VMAT (two patients in RayStation 5.0) were anonymized and re-planned with STD-VMAT and the other MCO modality — MCO-VMAT in RayStation v4.7 for the eight patients originally receiving MCO-IMRT, and MCO-IMRT RayStation v5.0 for the two patients treated by MCO-VMAT. The vendor (RaySearch Laboratories, Stockholm, Sweden) has not changed the IMRT optimization algorithm since RayStation v4.0, and VMAT since v4.7, which has been validated by our institutional experiences. Therefore, it was not necessary to re-optimize all plans in the latest version.

2.B | Computed tomography simulation

Computed tomography (CT) data were originally prepared based on the RTOG 0933 criteria. All patients had MRI with axial T2-weighted and gadolinium contrast-enhanced T1-weighted sequences for hippocampus contouring with slice thickness no greater than 1.5 mm. They were immobilized in the supine position with a thermoplastic mask for a CT simulation with slice thickness of 1.25 mm with intravenous contrast. The MRI images were semi-automatically fused to the simulation CT by an attending radiation oncologist in MIM Vista version 6 (MIM Software Inc., Cleveland, OH). Target structures (such as whole brain and distinguishable metastatic lesions), organs-at-risk (OARs) and external patient contour w/immobilization devices were also contoured within MIM before exporting to the treatment planning system (TPS). The hippocampus was contoured based on the RTOG contouring guidelines. The hippocampal avoidance region was generated by a 5 mm contour expansion followed by a secondary 5 mm expansion to control the dose gradient in the avoidance region. There were up to two levels of planning target volume (PTV). The hippocampal sparing whole brain PTV included the whole brain parenchyma to C1 or C2 as the clinical target volume (CTV) plus 2 mm expansion with subtraction of the hippocampal avoidance regions. The metastatic PTV was expanded from the delineated metastatic lesions with a 2 mm expansion.

2.C | Treatment prescription

Ten patients received 30 Gy in 15 fractions to the hippocampal sparing whole brain PTV (PTV30) with an SIB of 37.5 Gy to specific metastatic PTV (PTV37.5).

2.D | Custom optimization contours

All plans were given custom contours to guide the optimization process. These contours included PTV30−PTV37.5, a volume used to

help improve dose uniformity within the whole brain region without metastatic disease. A custom target structure was created within PTV30 in between the left and right hippocampus for added control of midline target coverage. A custom avoidance structure was created inferior to the PTV30 to control excessive inferior dose to uninvolved optic regions and oral cavity.

2.E | Treatment plan parameters

MCO-IMRT plans utilized a step-and-shoot delivery method (SMLC) with eight to eleven beams at variable gantry angles (including one to three non-coplanar angles) depending on the location of the metastatic disease. All plans were optimized using a 6-MV photon beam on an Elekta Infinity linear accelerator employing Agility multileaf collimator (MLC, 80 pairs of 5-mm leaves).

All VMAT plans were generated using dual coplanar full arcs (clockwise/counterclockwise of 358°, between 181° and 179°), with a fixed collimator angle (between 20° to 40°) selected based on the angle of hippocampus. A third non-planar vertex arc swept from 1° to 179° with a 270° couch kick. All three arcs employed a control point every 2° of gantry rotation. The dose grid resolution for all plans was set to $0.2 \times 0.25 \times 0.2$ cm^3 (left-right, superior-inferior, and anterior-posterior, respectively).

The use of multiple arcs has been shown to yield superior plan quality.[22] Furthermore, with the dual arc feature enabled, only one set of fluence profiles are optimized while more information from the fluence maps can be kept during the leaf sequencing process. This 'one arc' fluence map conserves leaf motion with one arc focusing on the left side of the target and the second arc on the right side at a given control point angle, which in turn reduces the leaf openings over the OAR and increases sparing.[23] Chen et al. reported that the use of dual arcs in VMAT resulted in notable dosimetric improvements for complex targets such as head and neck.[24]

The differences between the STD-VMAT (a.k.a., rayArc) and MCO-VMAT optimization in RayStation were explained by Ghandour et al.[25] The rayArc uses a direct machine parameter optimization (DMPO) algorithm that starts with a coarse arc segmentation (24° spacing), while converting to optimized fluence maps per initial angle. The maps are then converted into a user determined 2–4 control points per initial angle, while filtering out the smallest points based on a sorting algorithm.[23] Control points are then converted to comply with machine parameter motion constraints (e.g., max leaf speed, valid dose rates, delivery time, number of monitor units per degree) along with leaf/jaw positioning (static or dynamic). Chen et al. reported the use of small arc spacing of 2° per control point led to notable dosimetric improvements for complex targets such as head and neck.[24]

MCO empowers the user to produce a final plan by considering multiple criteria via the generation of a Pareto database followed by a navigation process which smoothly interpolates amongst the plans in the database. For a Pareto optimal plan, no criterion can be further improved without sacrificing another criterion. For photon optimization in RayStation, for a plan with n objectives defined, a minimum of 2*n* Pareto plans are needed to produce a practical approximation of the Pareto surface,[18] whereas the use of 4n plans leads to a closer approximation to the true Pareto surface, which we use at our institute.[19] In addition to objectives, constraints are used to focus on clinically useful plans, creating a Pareto surface with smaller range but finer resolution. At least two constraints — the minimum dose for a target and the maximum dose for an organ, are required to start the Pareto plan generation. An MCO plan is selected by navigating on the Pareto surface using the navigational sliders. A particular slider can be clamped to limit the range of navigation on the Pareto surface to prevent degradation while navigating other sliders in desired directions. Once navigated, the fluence pattern of the selected Pareto optimal plan is converted to deliverable machine parameters for each control point using a final dose calculation. In RayStation, this final deliverable plan is used for clinical evaluation.

MCO-VMAT uses three unique algorithms: a convex Pareto surface approximation for fluence maps, a fluence map optimization for the discrete Pareto surface representation (navigational best plan) and DMPO VMAT optimization to generate MLC segments.[25] Both VMAT optimization techniques used a single-value pencil beam kernel decomposition for approximation to save computational time. An intermediate dose is used to minimize discrepancies between pencil beam and collapsed cone algorithm (which is used in final dose calculation).[25]

2.F | Dosimetric and plan quality comparison analysis

2.F.1 | Organs-at-risk

With regards to hippocampal sparing, four metrics were assessed to determine plan quality: dose covering 100% volume (D100), mean dose (Dmean), point max of hippocampus (Dmax) and percent volume receiving 10 Gy (V10). Combined lens dose and cochlea dose (left and right) are assessed by point max (Dmax).

2.F.2 | Target coverage

The coverage of PTV30 was assessed by percentage of volume receiving 25 Gy (V25) and 30 Gy (V30), whereas the coverage of PTV37.5 and GTV37.5 was evaluated using dose covering 95% (D95) and 99% (D99) of the volume, respectively.

2.F.3 | Plan quality parameters

Total monitor units and Dmax (Gy) for each plan was recorded. Dose uniformity with control of the dose falloff was assessed using the volume of PTV30−PTV37.5. The V35 of PTV30 was also recorded to determine the control of dose beyond 30 Gy in the whole brain regions without metastatic disease.

2.F.4 | Statistical analysis

Statistical analysis was performed with a Wilcoxon signed-rank test to determine if there was any significant difference of the

parameters examined along with standard deviations (SD). A P value smaller than 0.05 was considered statistically significant. The comparison was conducted between MCO-VMAT and MCO-IMRT, as well as between MCO-VMAT and STD-VMAT. STD-VMAT was not compared to MCO-IMRT.

3 | RESULTS

Table 1 shows the total plan MU, dose to OARs, maximum plan dose, and target coverage for the ten patients. The number of metastatic lesions, the size of the PTV and their proximity to the hippocampus are also shown along with the coverage of the metastatic PTV (PTV37.5). The results are shown for MCO-VMAT (MV), MCO-IMRT (MI), and STD-VMAT (SV).

Table 2 shows the cumulative averages of the metrics illustrated in Table 1 for each treatment modality. The results for the MCO-VMAT are compared to MCO-IMRT and STD-VMAT separately, to demonstrate any improvements resulted in by the use of MCO and VMAT, respectively.

3.A | OAR sparing

As shown in Table 2, the cumulative averages of D100 and Dmean for hippocampus were both lower for MCO-VMAT compared to STD-VMAT or MCO-IMRT. Dmax to hippocampus was similar in all three modalities. Decrease in hippocampus D100 using MCO-VMAT was statistically significant when compared to STD-VMAT. Cumulative averages of the maximum dose to the lenses and that to the cochleas were lower for MCO-VMAT, when compared to either STD-VMAT or MCO-IMRT.

3.B | Target coverage

As shown in Table 2, MCO-VMAT achieved statistically significant improvement on prescription coverage for PTV30 when compared to either MCO-IMRT or STD-VMAT, while maintaining lower OAR values. The standard deviation of the V30 is also smaller for MCO-VMAT, implying improved uniformity of plan quality. The use of VMAT instead of IMRT in MCO planning resulted in an improvement of 14.2% for the V30 of PTV30, and the use of MCO for VMAT optimization led to a net gain of 4.8%. For the ten patients with metastatic disease, MCO-VMAT provided higher D95 and D99 for PTV37.5, with the results being statistically significant for D95 difference between MCO-IMRT and STD-VMAT.

Figure 1 compares the coronal view of the isodose distribution provided by the three modalities for the patient that MCO-VMAT demonstrated most improvement on V30 of PTV30 (patient 3 in Table 1). For this patient, only 43.5% of the PTV30 was covered by the prescription dose in MCO-IMRT, and 82.5% in STD-VMAT. The use of MCO-VMAT promoted the coverage to 95.4%, which is generally considered clinically desirable.

Figures 2 and 3 show the dosimetric performance of the three modalities for the patient with the maximum number of metastatic lesions (12 for patient 6 as shown in Table 1). Figure 2 shows the D99 of GTV37.5 and D95 for PTV37.5. In general, the three modalities provided similar target coverage considering the challenges of multiple lesions. Figure 3 compares the dose volume histogram (DVH) for various target volumes and normal organs. Both MCO- and STD-VMAT created lower hotspots in the whole brain and spared more hippocampus than MCO-IMRT. MCO-VMAT and MCO-IMRT led to lower dose to the lens. MCO-VMAT significantly reduced the dose to the combined cochleas compared to the other two modalities. Overall, MCO-VMAT offered the best combination of target coverage and normal tissue sparing for this most challenging case.

3.C | Treatment plan quality parameters

On average, MCO-VMAT resulted in a lower overall plan Dmax hotspot. The decrease was 1.2 Gy and 1.8 Gy when compared to MCO-IMRT ($P = 0.047$) or STD-VMAT ($P < 0.01$), respectively. Dose

TABLE 1 Comparison of plan performance for the ten SIB HA-WBRT patients. MV stands for MCO-VMAT, MI for MCO-IMRT, and SV for STD-VMAT.

		1			2			3			4			5			6			7			8			9			10		
		MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV	MV	MI	SV
Total MU		673	1143	1115	734	1133	1087	807	1056	1161	690	975	1077	737	1265	1026	793	1149	1186	755	1274	1043	773	1138	1148	808	1386	1258	699	1399	1422
Hippocampus	**D100 (Gy)**	8.1	7.3	8.0	7.5	7.6	8.3	7.5	8.1	8.0	7.1	7.8	8.5	7.6	9.6	7.7	8.1	10.5	7.8	7.4	7.8	8.0	7.6	7.1	7.9	8.4	7.8	8.5	8.7	9.0	9.1
	Dmean (Gy)	9.0	8.1	9.1	8.8	9.1	9.8	9.0	9.0	9.2	8.6	9.5	9.4	9.2	11.3	9.0	9.6	13.0	9.1	8.3	9.5	9.0	8.6	8.8	8.9	10.0	9.6	9.6	10.5	10.6	10.2
	Dmax (Gy)	13.9	12.6	14.6	17.1	17.9	15.9	16.8	13.1	14.9	16.5	16.1	15.8	16.8	16.2	15.8	16.8	16.7	15.0	12.7	14.5	13.5	15.0	16.1	13.9	17.7	19.3	20.0	16.1	17.4	17.9
	V10 (%)	6.5	1.8	5.5	10.8	18.5	30.2	15.1	5.5	14.6	12.0	25.8	19.4	16.1	91.9	10.4	23.3	15.4	11.6	24.7	100	14.1	4.5	21.0	13.7	42.2	26.5	31.2	63.9	64.7	46.1
Lenses	**Dmax (Gy)**	7.1	7.2	7.2	7.2	8.3	7.6	6.2	6.6	7.6	6.8	4.4	7.4	6.5	8.8	7.3	7.1	8.6	7.3	7.7	6.9	7.2	8.9	5.9	7.1	4.5	8.4	7.1	8.2	12.1	7.3
Cochleas	**Dmax (Gy)**	25.7	21.8	21.3	23.3	22.4	22.0	15.3	30.6	25.0	18.0	17.8	24.6	20.2	25.7	20.8	19.8	30.4	21.3	23.2	29.3	23.4	21.2	23.5	21.2	16.0	23.8	20.9	18.1	22.0	21.5
Plan Max Point	**Dmax (Gy)**	39.5	40.2	41.8	39.8	39.2	40.7	38.6	40.0	41.4	39.8	41.2	42.3	40.9	42.3	41.4	40.5	40.3	41.1	39.0	38.2	41.4	39.5	41.0	47.2	39.6	42.5	41.5	39.4	40.1	40.8
PTV30	**V25 (%)**	99.2	98.7	97.9	97.2	97.2	96.7	99.7	98.6	98.0	97.3	97.9	97.9	99.2	98.9	99.1	99.4	99.8	98.5	98.9	95.3	99.1	99.7	98.3	99.1	99.7	97.4	99.5	99.7	99.9	99.2
	V30 (%)	92.3	82.3	82.3	91.6	90.0	89.6	95.4	43.5	82.5	92.1	89.8	84.6	94.5	82.7	85.7	94.0	91.9	86.7	94.3	51.0	94.7	91.7	81.7	86.7	92.8	81.8	93.0	88.8	90.2	93.6
PTV37.5	**D95 (Gy)**	37.8	37.5	37.5	37.7	37.6	37.5	37.5	37.1	36.8	36.5	36.9	36.2	37.6	36.7	37.2	37.3	37.1	37.3	37.8	37.6	37.7	37.7	37.2	37.0	37.5	37.5	36.6	37.3	35.5	37.4
GTV37.5	**D99 (Gy)**	37.8	37.7	37.2	37.8	37.7	37.9	37.4	37.1	37.3	36.0	37.7	34.7	37.4	37.5	37.0	37.9	36.8	38.1	37.9	37.5	38.7	37.7	37.1	36.2	37.6	38.2	37.0	38.0	35.5	37.8
PTV30-PTV37.5	**V35 (%)**	1.9	1.0	2.4	1.4	2.3	1.6	1.4	0.3	3.6	2.2	3.9	1.9	4.8	0.5	1.4	1.5	9.1	1.7	0.9	0.7	1.9	0.9	2.1	1.4	6.3	7.4	2.9	5.3	3.9	4.1
Total PTV 37.5	**cc**	70.2			7.6			16.6			8.6			16.6			3.9			0.6			25.0			74.9			23.3		
Prox of PTV 37.5	**mm**	22.7			26.1			18.0			6.0			1.3			21.8			60.0			8.2			15.0			25.0		
Number of lesions		1			1			3			1			3			12			1			1			11			5		

TABLE 2 Cumulative average and standard deviation of the plan metrics shown in Table 1, for each treatment modality. The impact of using VMAT over IMRT in MCO planning is shown under the MCO column, whereas the impact of using MCO over standard optimization in VMAT planning is shown in the column of VMAT. The differences with statistical significance ($P < 0.05$) is shown in red.

					MCO		VMAT	
					VMAT minus IMRT		MCO minus STD	
Combined Averages		MCO-VMAT	MCO-IMRT	STD-VMAT	Δ	p	Δ	p
TOTAL MU		746.9 ± 46.3	1191.8 ± 129.9	1152.3 ± 111.5	-444.9	<0.01	-405.4	<0.01
PTV30-PTV37.5	V35 (%)	2.7 ± 1.9	3.1 ± 2.9	2.3 ± 0.9	-0.4	0.802	0.4	0.881
Hippocampus	D100 (Gy)	7.8 ± 0.5	8.2 ± 1.0	8.2 ± 0.4	-0.4	0.332	-0.4	0.046
	Dmean (Gy)	9.1 ± 0.7	9.8 ± 1.4	9.3 ± 0.4	-0.7	0.114	-0.2	0.384
	Dmax (Gy)	15.9 ± 1.5	16.0 ± 2.0	15.7 ± 1.8	-0.1	0.575	0.2	0.646
	V10 (%)	21.9 ± 17.4	37.1 ± 33.6	19.7 ± 11.7	-15.2	0.332	2.2	0.384
Lenses	Dmax (Gy)	7.0 ± 1.1	7.7 ± 2.0	7.3 ± 0.2	-0.7	0.330	-0.3	0.044
Cochleas	Dmax (Gy)	20.1 ± 3.2	24.7 ± 4.0	22.2 ± 1.5	-4.6	0.046	-2.1	0.011
PTV30	V25 (%)	99.0 ± 0.92	98.2 ± 1.3	98.5 ± 0.8	0.8	0.139	0.5	0.075
	V30 (%)	92.7 ± 1.8	78.5 ± 16.2	87.9 ± 4.3	14.2	<0.01	4.8	0.036
PTV37.5	D95 (Gy)	37.5 ± 0.3	37.1 ± 0.6	37.1 ± 0.4	0.4	0.047	0.4	0.012
GTV37.5	D99 (Gy)	37.5 ± 0.5	37.3 ± 0.7	37.2 ± 1..1	0.2	0.384	0.3	0.139
Dmax	Dmax (Gy)	39.7 ± 0.6	40.5 ± 1.2	42.0 ± 1.8	-0.8	0.047	-2.3	<0.01

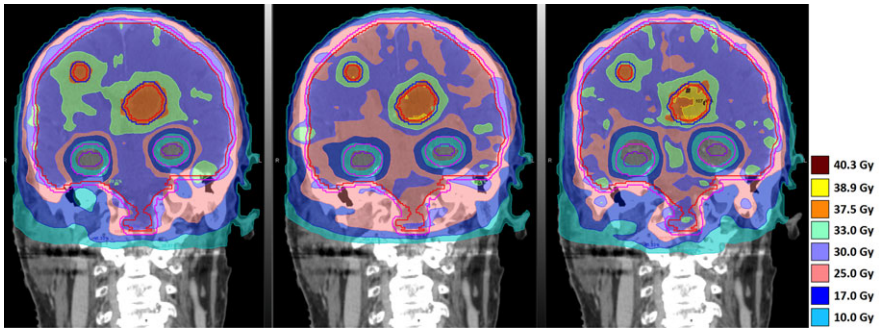

FIG. 1. Isodose plan comparison in the coronal view for the patient that MCO-VMAT demonstrated most improvement on the coverage of the whole brain PTV30 (patient 3 in Table 1).

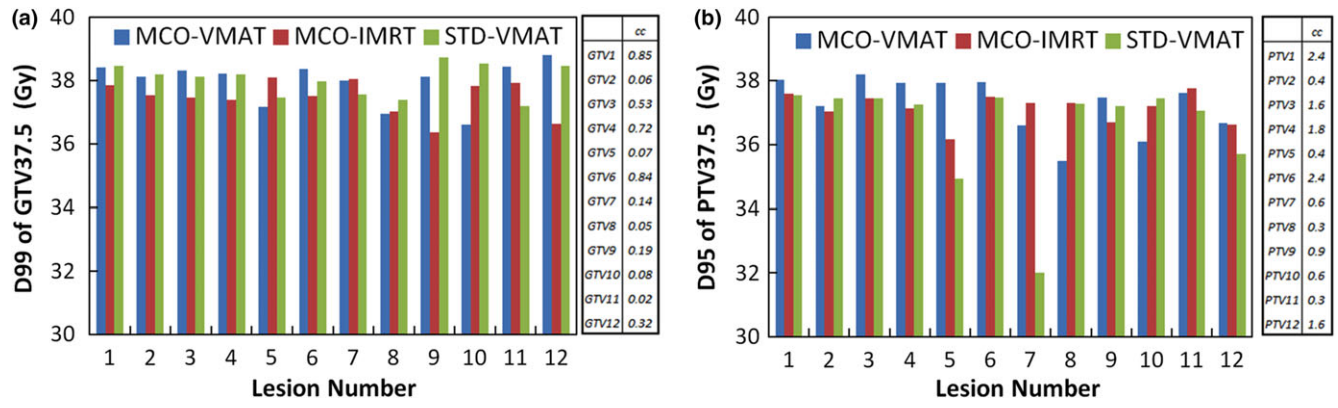

FIG. 2. Comparison of target coverage provided by MCO-VMAT, MCO-IMRT and STD-VMAT, for the patient with 12 metastatic lesions (patient 6). The results are shown for the (a) D99 of the metastatic GTV (GTV37.5) and (b) D95 of the metastatic PTV (PTV37.5) that receive the SIB. The target volumes are shown beside the charts.

uniformity, quantified by the volume receiving 35 Gy with the PTV30 but outside PTV37.5, observed MCO-VMAT (2.7%), when compared to MCO-IMRT (3.1%) or STD-VMAT (2.3%). A significant decrease was observed for the average monitor unit (MU) for MCO-VMAT (746.9), when compared to MCO-IMRT (1191.8) or STD-VMAT (1152.3). The reduction was 37% and 35%, respectively ($P < 0.01$ for both.)

4 | DISCUSSION

All MCO-VMAT plans (with or without the SIB to the metastatic lesions) achieved the RTOG 0933 guidelines (which only required WBRT to 30 Gy) with acceptable or better hippocampus sparing.[26] Prior studies have highlighted MCO for its operational flexibility and planning efficiency, along with superior dosimetric performance.[21,24]

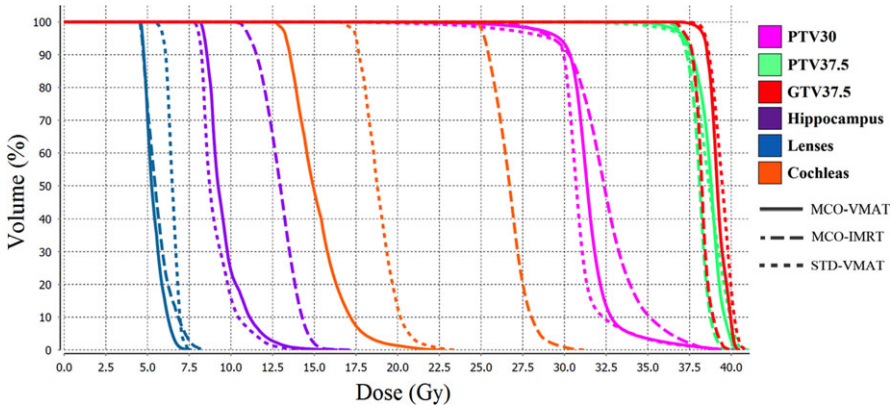

FIG. 3. Dose volume histogram (DVH) for the patient illustrated in Fig. 2 (patient 6). The PTV37.5 and GTV37.5 are combined volumes for the 12 lesions.

With the navigation function in MCO, metrics such as dose uniformity and maximum dose can be loosened for the potential of greater OAR sparing or more target coverage. In this HA-WBRT study, the constraints were customized based on the hippocampus volume, the number, size and location of any metastatic lesions, to allow the generation of the Pareto surface from a favorable starting position. As reported in prior studies, if the navigation is done in a very unbalanced manner or pushed towards extreme values, dose discrepancy will appear at the MLC segmentation stage when the optimizer tries to find the MLC pattern physically allowed by the linear accelerator that can mimic the fluence map achieved at the end of the navigation step.[21] The discrepancy is also attributed to the difference in dose calculation algorithm — pencil beam in Pareto optimization and the more accurate collapsed cone in final dose calculation after the MLC segmentation. The possibility of real-time navigation using a spectrum of Pareto-optimal plans can lower the learning curve for planning staff and thus encourage more clinics to consider highly conformal treatment (e.g., SIB with VMAT) in very complex anatomical situations (e.g., hippocampal sparing, limbic circuit sparing).[7,27]

Prokic et al. reported that the SIB technique could achieve better hippocampal sparing compared to sequential boost in form of stereotactic radiation therapy (e.g., 8 Gy × 2) after WBRT.[28] In addition, the use of a single isocenter for the treatment of multiple brain metastasis led to reduced delivery time while maintaining the dosimetry quality, as compared to the sequential boost.[29] Our study demonstrates that MCO-VMAT allows for hippocampal sparing despite a variety of SIB conditions (number of lesions, size of targets and proximity to hippocampus). Also, the SIB approach allowed selective dose escalation for lesions within less than 5 mm to the hippocampus which would otherwise be rejected for protocol. As reported by Gondi et al., 3% of brain metastases in 8.6% of patients were found within 5 mm of the hippocampus (n = 371). [30] In our study, MCO-VMAT achieved dose escalation to 37.5 Gy for lesions as close as 1.3 mm from the hippocampus (patient 5). This example shows the potential tradeoffs between target coverage and OAR sparing, as controlling metastatic burden is also a key factor in neurocognitive outcomes.[31] In this case, both MCO modalities increased PTV 37.5 SIB target coverage for the tumor in close proximity to the hippocampus. However, MCO-VMAT offered 95% coverage for PTV30, whereas MCO-IMRT and STD-VMAT only provided 83% and 86%, respectively, with comparable hippocampus metrics as shown in Table 1. MCO allowed user flexibility for clinicians to prioritize high-risk target clinical objectives utilizing Pareto optimal navigational solutions. Thus, SIB with MCO-VMAT may allow for meaningful hippocampal sparing for patients who would otherwise not be eligible due to peri-hippocampal metastases.

5 | CONCLUSION

MCO-VMAT was proven superior to MCO-IMRT or STD-VMAT for HA-WBRT. This study sampled patients with various numbers of metastatic lesions (0 to 12), and the lesions had a wide variety of size and location with respect to the hippocampus. On average, MCO-VMAT improved the PTV30 coverage, with statistical significance, by 14.2% and 4.8%, respectively, compared to MCO-IMRT and STD-VMAT. It also slightly boosted the dose to GTV37.5 and PTV37.5. Finally, MCO-VMAT significantly reduced the MUs, resulting in faster treatment compared to both MCO-IMRT and STD-VMAT.

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CONFLICT OF INTEREST

The authors declare no conflict of interest to disclose.

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