Dosimetric Comparison of Four Volumetric-Modulated Arc Therapy Beam Arrangements Utilized for Hippocampal-Sparing Whole-Brain Radiation Therapy

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Abstract

Purpose: In the present study, the performance of four VMAT beam arrangements used for hippocampal-sparing whole-brain radiation therapy is addressed. **Material and Methods:** Data corresponding to 20 patients were utilized so as to generate plans for every beam configuration. A preliminary study was conducted to assess the optimal distance between optimization structures (PTVx) and hippocampi. V_{25}, V_{30}, $D_{50\%}$, $D_{2\%}$, $D_{98\%}$, homogeneity index (HI) and Paddick conformity factor (CF) were evaluated for PTV. $D_{100\%}$ and D_{max} were considered for hippocampi. All plans were required to perform at least as recommended in RTOG 0933 trial regarding organs at risk (OAR) sparing and PTV objectives. **Results:** Considerable hippocampi sparing alongside with a reasonably low decrease in PTV coverage was achieved using a 7 mm distance between hippocampi and PTV optimization structure. Beam setup 3 (comprised of two full arcs with 0º couch angle and two half arcs with 90º couch angle) achieved the best PTV coverage, HI and CF, while it performed the second-best sparing in hippocampi and lenses. Moreover, beam setup 3 was the second-fastest treatment, although it resulted in the highest number of delivered MU among all beam setups. Beam setup 1 (comprised of two full arcs with no couch angles) was the fastest and it delivered a significantly less amount of monitor units compared with the other beam setups evaluated. Furthermore, a higher robustness was obtained by using no couch angles. Although beam setup 1 was the least optimal considering OAR sparing, it still performed better than required in the RTOG 0933 trial. **Conclusions:** Overall, beam setup 3 was considered to be the best. It is worth mentioning that, apart from our results, the election of one of these beam arrangements might be dependent on the amount of patient workload at a specific institution.

Keywords: Hippocampal sparing, Radiation Therapy Oncology Group 0933 trial, volumetric-modulated arc therapy, whole-brain irradiation

INTRODUCTION

Whole-brain radiation therapy (WBRT) is a well-established radiation therapy at multiple settings of oncology management. For patients with brain metastases, it is the most used treatment option[1-3] to control visible tumors and micrometastases.[4] Furthermore, WBRT is typically used as a prophylaxis for limited-stage small cell lung cancer[4] as well as during the treatment of pediatric central nervous malignancies.[5]

In patients suffering from brain tumors, WBRT helps reduce intracranial pressure, achieving rapid palliation of neurological symptoms. Besides, this treatment option improves local tumor control as an adjuvant to surgery or radiosurgery[6] as well as increasing survival when tumor regression occurs.[7] Unfortunately, it has been shown that WBRT might be correlated with long-term, progressive, and irreversible neurologic sequelae[8] such as dementia,[9] cerebellar dysfunction,[10] and neurocognitive function decline (NCFD). Recent publications also suggested that NCFD symptoms such as short-term memory loss and a reduced concentration capability could be apparent months after WBRT.[11]

Over the past decades, it has been established that the hippocampus is an essential actor in memory function.[12] There

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is mounting evidence that radiation-induced hippocampal injury is responsible for NCFD and other side effects.[13] More specifically, these side effects might be due to the damage of neural progenitor cells, located in the dentate gyrus of the hippocampus, which are particularly sensitive to radiation. In fact, small doses of radiation might cause apoptosis in the subgranular zone of the dentate gyrus even when no such apoptosis is observed in other brain areas.[14] It has been shown that radiation-induced damage to rat hippocampus led to structural impairment in the environment of neural progenitor cells. As a result, these cells became less proliferative. Furthermore, damage of rat hippocampus also led to alterations in cell differentiation.[14-18] The reduction of neurogenesis in the subgranular zone,[14,18,19] as well as the alteration of cell differentiation induced by WBRT is thought to be responsible for the decline in hippocampal-related cognitive functions.[15,16,20]

Hippocampal-sparing whole-brain radiation therapy (HS-WBRT) has been proposed to minimize the NCFD in patients. Thanks to great advancement in radiotherapy techniques, namely, volumetric-modulated arc therapy (VMAT) or helical tomotherapy, it has been possible to spare hippocampal areas without a substantial loss in dose homogeneity and conformity.[21-23] Several recent publications reported planning results utilizing VMAT,[24-29] intensity-modulated radiation therapy,[26,27,30] and tomotherapy.[21,31] There are also published results demonstrating dosimetric improvements achieved by optimizing the patient positioning.[32]

Although sparing hippocampal structures is recommended to reduce NCFD, the main treatment objective is to achieve an adequate dose distribution in the brain to avoid tumor growth. Avoiding hippocampal regions poses a risk of diminishing the effectiveness of HS-WBRT when metastases nearby these structures are present. In such cases, HS-WBRT might not be an eligible treatment. However, in a study including 100 patients with 272 metastases, the risk of finding a metastatic lesion within 5 mm of hippocampi was <16%.[33] Another recent study that included a total of 371 patients and 1133 metastases showed that only <9% of patients had metastases within a 5 mm distance from hippocampi.[34] Hence, HS-WBRT might be a suitable treatment option for ≥90% of metastatic patients undergoing WBRT.

Considering these results, it has been proposed to apply a 5 mm margin to hippocampi to create hippocampal avoidance regions.[34] However, due to the location of the hippocampi in the brain, treatment planning of HS-WBRT is challenging.

Recently, HS-WBRT for brain metastases has been evaluated in a prospective phase II study (Radiation Therapy Oncology Group [RTOG] 0933[35]) and would be in the forthcoming NRG-CC001 phase III trial. Both studies have been designed to deliver 30 Gy in ten fractions to the whole-brain clinical target volume, excluding a 5 mm hippocampal avoidance region. Strict constraints to target coverage as well as to organs at risk (OAR) doses were defined in the RTOG 0933 protocol.

The NRG protocol uses the same guidelines as the RTOG 0933 protocol regarding optimization, contouring, and imaging.

The main objective of this study is to evaluate the dosimetric performance of four different VMAT beam arrangements designed for HS-WBRT with respect to RTOG 0933 dose criteria. In addition, the distance between the planning target volume (PTV) optimization structure and the hippocampi is studied.

MATERIALS AND METHODS

Patients and contouring

A total of 20 eligible patients for HS-WBRT were selected for the study. Imaging of each patient consisted of a 3 mm slice thickness computed tomography (CT) scan employing a Philips Brilliance Big Bore (Philips Healthcare, Amsterdam, The Netherlands) and a T1-weighted magnetic resonance image utilizing a 3T Diamond Select Achieva (Philips Healthcare, Amsterdam, The Netherlands). To minimize the patient motion, a thermoplastic mask was utilized. Reference marks were placed on every patient mask to improve treatment reproducibility. The magnetic resonance and the CT images were fused to facilitate hippocampal contouring. Hippocampi were contoured according to the RTOG 0933 contouring atlas. Hippocampal avoidance regions were defined as a 5 mm expansion of both hippocampus. Optic chiasm, optic nerves, eyes, lenses, and brainstem were also contoured. Evaluation PTV (PTV_{eval}) was defined as the usual WBRT PTV minus the hippocampal avoidance regions. This volume was used to evaluate final results yielded by every calculated treatment plan, as suggested by RTOG 0933 trial.[35] For optimization purposes, several additional volumes were created: a 5 mm thick ring separated 2 mm from the WBRT PTV to control high dose extension and the distance between the optimization structure (PTVx), a set of structures defined as the WBRT PTV minus the hippocampi expanded x mm in three dimensions. The x value was varied between 5 and 9 mm in 1 mm steps and it represents PTVx and the hippocampi. As it can be seen, PTV5 is the same structure as PTV_{eval} defined above, although they have different purposes. The former is just an optimization structure while the latter is the PTV defined by RTOG 0933[35] to evaluate treatment plan results.

Treatment planning

Treatment plans were created in Eclipse v. 11.0 TPS (Varian Medical Systems, Palo Alto, CA, USA) using a 6 MV Varian Unique linac having a maximum dose rate of 600 monitor units (MU)/min and a Millennium 120 multi-leaf collimator. The anisotropic analytical algorithm was used alongside with the Progressive Resolution Optimizer (version 11.031) for VMAT optimization. Four distinct VMAT beam setups were considered. For each patient, the four plans were created following the beam arrangements described in Table 1. Every plan was optimized according to the same parameters regarding the optimization cost function (weights, dose limits, and dose objectives), subsequently minimizing the possible effects

that might be introduced by means of distinct optimization procedures.

Each patient was prescribed a total of 30 Gy to the PTV_{eval} in 10 fractions (3 Gy per fraction). Dose limits for OAR and dose objectives for PTV_{eval} were defined following the RTOG 0933 protocol.[35] A preliminary study was conducted with the purpose of evaluating the optimum optimization structure (PTVx) so as to obtain a considerable hippocampi dose reduction, while maintaining a reasonable PTV_{eval} coverage. To this end, five PTV optimization structures (referred to as PTV5, PTV6, PTV7, PTV8, and PTV9) were created as mentioned in the previous subsection. Such analysis was performed utilizing data from seven patients and employing the four beam arrangements appearing in Table 1. As a result of this preliminary study, it was decided to use PTV7 as the optimization structure for all plans utilized in the beam setup comparison with data from 20 patients. A compromise between an acceptable PTV_{eval} coverage and a significant reduction in hippocampal doses must be achieved. For this purpose, three new variables (ΔD_{max}, $\Delta D_{100\%}$, and ΔV_{30}) are defined as the differences between cases 5 and 7 (5–7) and between cases 7 and 9 (7–9), respectively. Case 5 refers to results obtained when optimizing using PTV5 as the optimization structure (same for cases 7 and 9, respectively). For each pair of cases considered, namely, 5–7 and 7–9, ΔD_{max} and $\Delta D_{100\%}$ are referred to hippocampi and ΔV_{30} is referred to PTV_{eval}.

Plan evaluation

To evaluate the fulfillment of the dose constrains and PTV_{eval} coverage recommended by the RTOG 0933 protocol, the following parameters were considered. First, PTV_{eval} volumes receiving 25 Gy (V_{25}) and 30 Gy (V_{30}) were determined. Second, the dose received by 2% ($D_{2\%}$), 50% ($D_{50\%}$), and 98% ($D_{98\%}$) of the PTV_{eval} volume were assessed. Furthermore,

the homogeneity index (HI) defined as in International Commission on Radiation Units report 83[36] and the Paddick conformity factor (CF)[37] were calculated to evaluate dose homogeneity and dose conformity, respectively. Regarding OAR, the D_{max} to optic nerves, optic chiasm, brainstem, lenses, eyes, and hippocampi was determined. Finally, the minimum dose ($D_{100\%}$) to hippocampi and the average dose (D_{avg}) to eyes were also evaluated.

Statistical analysis

Data appearing in subsequent tables are expressed as the average values considering all patients involved (seven patients in the preliminary PTVx study and 20 patients in the beam setups comparison). Moreover, the uncertainty is addressed by the standard deviation multiplied by a coverage factor ($k = 2$). To evaluate the statistical significance of the results, a two-tailed paired samples Student's t-test was applied. $P = 0.05$ was chosen as the level of significance so as to demonstrate if the results yielded by one beam arrangement are statistically significant with respect to those obtained by other beam setups. This means that, if a P value obtained of two beam setup comparison is lower than 0.05, these two beam setups are different at 95% confidence level regarding the variable for which the t-test was performed.
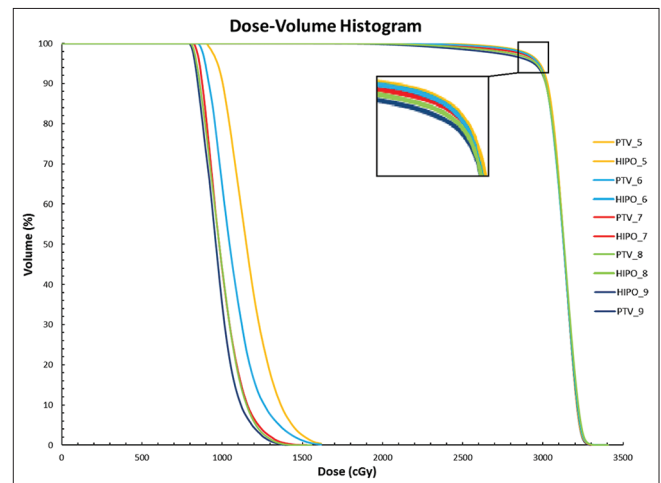
RESULTS

Target optimization structure study

The results obtained from the analysis performed are presented in Table 2. The major differences among distinct beam setups were mainly focused on hippocampi D_{max} and $D_{100\%}$ and on PTV_{eval} coverage, quantified in this study by the V_{30} parameter. Figure 1 shows the dose-volume histogram (DVH) curves observed for hippocampi and PTV_{eval} in the five different plans investigated (i. e., those plans having PTV5 to PTV9

Table 1: Gantry, collimator, and couch angles for beam arrangements considered

Setup number	Gantry angles (°)	Collimator angle (°)	Couch angle (°)
1	A1: 181-179 (CW)	30	0
	A2: 179-181 (CCW)	330	0
2	A1: 181-179 (CW)	30	0
	A2: 179-181 (CCW)	330	0
	A3: 181-350 (CW)	30	300
	A4: 10-179 (CCW)	330	60
3	A1: 181-179 (CW)	30	0
	A2: 179-181 (CCW)	330	0
	A3: 21-179 (CW)	150	90
	A4: 179-21 (CCW)	210	90
4	A1:181-179 (CW)	30	0
	A2: 179-181 (CCW)	330	0
	A3: 60-179 (CW)	30	30
	A4: 300-181 (CCW)	330	330
	A5: 181-300 (CW)	275	270

CW: Clockwise, CCW: Counterclockwise, A: Arc

Figure 1: Average dose-volume histogram plan comparison for beam arrangement 1 with distinct structures as targets (PTVx). Bilateral hippocampal structures and evaluation planning target volume results corresponding to the same plan are depicted as same color lines

Table 2: Results obtained for hippocampi maximum dose and minimum dose, respectively and planning target volume for evaluation coverage (expressed by the volume receiving 30 Gy, namely, V$_{30}$) for the four beam setups studied when utilizing distinct PTVx structures as optimization targets

Setup number	PTVx	Hippocampi		PTV$_{eval}$ V$_{30}$ (%)
		D$_{max}$ (cGy)	D$_{100\%}$ (cGy)	
1	5	1821.5±66.2	891.4±31.5	91.6±0.9
	6	1780.1±84.0	874.7±35.9	91.3±1.2
	7	1552.9±42.1	825.3±97.3	91.0±0.6
	8	1498.2±116.2	807.5±56.3	89.4±1.0
	9	1446.7±93.6	805.3±38.9	88.3±0.6
2	5	1764.5±116.7	828.9±43.6	92.8±0.9
	6	1684.2±82.0	797.0±84.2	92.7±0.6
	7	1484.6±91.4	770.6±78.1	92.5±1.8
	8	1465.3±117.3	764.1±54.6	91.2±0.8
	9	1445.5±118.7	753.2±61.2	89.6±1.3
3	5	1776.4±104.8	913.9±64.8	95.0±1.5
	6	1647.9±72.4	859.9±88.5	94.6±1.3
	7	1472.9±105.7	830.4±46.1	94.1±1.4
	8	1465.1±72.9	793.2±46.5	93.2±0.8
	9	1437.9±60.0	785.6±51.8	91.8±0.7
4	5	1845.2±76.9	964.6±102.2	93.1±1.6
	6	1724.9±71.5	881.0±87.9	93.0±0.7
	7	1554.2±104.6	878.2±45.2	92.4±1.0
	8	1510.6±84.4	814.4±64.6	90.8±1.1
	9	1487.5±79.2	797.2±51.3	89.7±0.7

Data are arranged as average values among 7 patients followed by the standard deviation multiplied by a coverage factor of 2. PTV$_{eval}$: Planning target volume for evaluation, D$_{max}$: Maximum dose, D$_{100\%}$: Minimum dose

Table 3: Differences in hippocampi maximum dose and minimum dose and differences in planning target volume for evaluation V$_{30}$ between PTVx cases 5 and 7 (5-7) and between PTVx cases 7 and 9 (7-9), respectively, for the four beam setups studied

Setup number	ΔPlan	Hippocampi		PTV$_{eval}$ ΔV$_{30}$ (%)
		ΔD$_{max}$ (cGy)	ΔD$_{100\%}$ (cGy)	
1	5-7	268.6±78.5	66.1±40.9	0.6±1.1
	7-9	106.2±102.6	20±41.9	2.7±0.8
	P	0.02	<0.01	<<0.01
2	5-7	279.9±148.2	58.3±35.8	0.3±2.0
	7-9	39.1±149.8	17.4±39.7	2.9±1.8
	P	0.02	<0.01	<<0.01
3	5-7	303.5±148.8	83.5±31.8	0.9±0.9
	7-9	35±121.5	44.8±27.7	2.3±1.1
	P	<<0.01	0.03	<0.01
4	5-7	291±108.2	86.4±74.5	0.7±1.5
	7-9	66.7±190.3	81±45.6	2.7±1.2
	P	0.02	0.58	<0.01

For each beam setup a comparison between both differences is established and the corresponding *P* value is shown. Data are arranged as average values among 7 patients followed by the standard deviation multiplied by a coverage factor of 2. PTV$_{eval}$: Planning target volume for evaluation, D$_{max}$: Maximum dose, D$_{100\%}$: Minimum dose

based on both D$_{100\%}$ and D$_{max}$ for each plan. The results are shown in Table 5.

Monitor units and overall treatment time

Table 6 summarizes the average MU required for every investigated VMAT beam arrangement as well as the average time employed to complete a fraction of the treatment (including beam on time and the amount of time that RTTs needed to move the couch).

Discussion

From Table 2 it can be noted that, as the x value was increased, both hippocampi doses (D$_{max}$ and D$_{100\%}$) and PTV$_{eval}$ coverage (V$_{30}$) decreased. This is a general trend for all four beam setups studied. If differences between D$_{max}$ results for PTVx and PTV(x + 1) cases are computed for hippocampi doses and the four beam setups, it can be shown that the dose reduction is significant ($P < 0.04$) when increasing x from 6 to 7 with respect to the case in which x is increased from 5 to 6. These differences are not significant for higher x values ($P > 0.65$). But if differences between cases 5 and 7 (5–7) and between cases 7 and 9 (7–9) are compared [Table 3], all *P* values are lower than 0.02. This means that the hippocampi D$_{max}$ reduction achieved is significantly higher when increasing x from 5 to 7 than when increasing x from 7 to 9 in the PTVx optimization structure. Regarding hippocampi D$_{100\%}$, there is no statistical significance when varying x from 5 to 6 compared to the case when x is varied from 6 to 7 ($P > 0.43$). For higher x values, the results are not significant either ($P > 0.78$). However, when comparing 5–7 and 7–9 results, Table 3 demonstrates that

optimization structures as targets) using beam setup 1. This DVH is the average obtained of seven patients' data.

As a general overview it can be noted that, as the distance from PTVx to hippocampi was increased (increasing x value), the PTV$_{eval}$ coverage (V$_{30}$) decreased as a result of dose reduction nearby the hippocampal avoidance regions. However, for the same reason, hippocampi D$_{max}$ and D$_{100\%}$ both decreased. With respect to the differences in hippocampi D$_{max}$ and D$_{100\%}$ and differences in PTV$_{eval}$ V$_{30}$ between PTVx cases 5 and 7 (5–7) and between PTVx cases 7 and 9 (7–9), the results obtained and the corresponding *P* values when comparing these differences are presented in Table 3.

Planning target volume results

For each plan, PTV$_{eval}$ V$_{25}$, V$_{30}$, D$_{50\%}$, D$_{2\%}$, D$_{98\%}$, HI, and CF were evaluated. PTV$_{eval}$ results obtained with different beam arrangements are reported in Table 4.

Organs at risk results

The results obtained for eyes and lenses doses are shown in Table 5. For both eyes, D$_{max}$ and D$_{avg}$ were considered, while for lenses only D$_{max}$ was documented. The results for optic nerves, brainstem, and optic chiasm are also reported in Table 5. Only D$_{max}$ was documented for them. Hippocampi were evaluated

Table 4: Planning target volume for evaluation results for every beam arrangement evaluated

				PTV$_{eval}$			
Setup number	V$_{25}$ (%)	V$_{30}$ (%)	D$_{50\%}$ (cGy)	D$_{2\%}$ (cGy)	D$_{98\%}$ (cGy)	HI	CF
1	99.0±0.6	90.6±1.4	3128.7±30.8	3250.7±8.7	2728.7±165.6	0.17±0.03	0.84±0.05
2	98.6±0.5	89.8±1.4	3115.2±19.5	3242.5±22.8	2625.8±103.1	0.20±0.02	0.82±0.06
3	99.3±0.5	94.2±2.3	3124.5±30.4	3248.1±40.7	2865.8±106.7	0.12±0.03	0.88±0.02
4	98.9±0.5	91.8±2.2	3132.3±12.1	3245.2±10.8	2720.5±157.6	0.17±0.04	0.87±0.03

V$_{25}$ and V$_{30}$ stand for the volume covered by 25 and 30 Gy, respectively, D$_{50\%}$, D$_{2\%}$ and D$_{98\%}$ stand for the dose received by 50%, 2%, and 98% of the volume. Data are arranged as average values among 20 patients followed by the standard deviation multiplied by a coverage factor of 2. HI: Homogeneity index, CF: Paddick conformity factor, PTV$_{eval}$: Planning target volume for evaluation

Table 5: Results obtained for eyes, lenses, hippocampi, chiasm, optic nerves, and brainstem doses for the four beam setups evaluated

Setup number	Left eye		Right eye		Left lens
	D$_{max}$ (cGy)	D$_{avg}$ (cGy)	D$_{max}$ (cGy)	D$_{avg}$ (cGy)	D$_{max}$ (cGy)
1	2018.7±222.4	1072.1±200.4	2037.0±165.5	1128.3±248.8	777.0±100.5
2	1742.4±240.8	917.9±109.7	1777.6±279.0	877.8±199.9	704.0±98.2
3	1804.7±221.2	923.8±204.2	1787.5±216.5	915.0±108.1	752.5±100.2
4	1912.8±187.8	882.3±202.0	1877.0±287.2	860.4±199.6	779.5±140.8

Setup number	Left hippocampus		Right hippocampus		Right lens
	D$_{100\%}$ (cGy)	D$_{max}$ (cGy)	D$_{100\%}$ (cGy)	D$_{max}$ (cGy)	D$_{max}$ (cGy)
1	896.7±59.3	1559.2±141.6	894.9±35.5	1541.5±75.6	786.2±221.0
2	835.0±64.1	1469.6±177.6	839.3±78.8	1410.1±126.9	709.1±95.8
3	872.3±35.6	1474.5±74.3	873.9±34.2	1416.7±142.4	763.8±113.3
4	890.4±65.2	1556.6±107.1	900.0±70.7	1466.1±127.0	785.3±98.6

Setup number	Optic nerves D$_{max}$ (cGy)	Brainstem D$_{max}$ (cGy)	Chiasm D$_{max}$ (cGy)
1	3316.5±65.4	3341.2±61.3	3264.3±97.8
2	3264.6±58.4	3375.8±58.5	3344.2±101.5
3	3266.0±105.4	3369.4±111.4	3339.5±86.8
4	3288.1±75.1	3395.3±113.9	3112.4±93.5

Data are arranged as average values among 20 patients followed by the standard deviation multiplied by a coverage factor of 2. D$_{max}$: Maximum dose, D$_{100\%}$: Minimum dose, D$_{avg}$: Average dose

Table 6: Average monitor units and average per fraction treatment time for the four beam setups considered

Setup number	MU	Treatment time (min)
1	680±38	2.51±0.32
2	725±54	5.63±0.51
3	848±60	4.52±0.64
4	757±88	6.51±0.58

Data are arranged as average values among 20 patients followed by the standard deviation multiplied by a coverage factor of 2. MU: Monitor unit

results are significant ($P < 0.03$) except for the beam setup 4 ($P = 0.58$). For beam setups 1–3, a significant D$_{100\%}$ reduction is achieved when utilizing PTV7 as optimization structure. With respect to PTV$_{eval}$ V$_{30}$, Table 3 data suggest, that for all beam setups considered, the coverage loss is significantly lower when comparing 5–7 and 7–9 results ($P < 0.01$). The above mentioned results justify the use of PTV7 as the preferred optimization structure if little PTV$_{eval}$ coverage loss and a significant hippocampi dose reduction are desired.

All four beam arrangements considered did fulfill the RTOG 0933 dose criteria. However, several differences among them were found. Considering PTV$_{eval}$ V$_{25}$ and V$_{30}$ values, beam setup 3 achieved the best results (99.3% ± 0.5% and 94.2% ± 2.3%, respectively). Besides, these results were statistically significant with respect to the other plans ($P = 0.03$ and $P < 0.01$ for V$_{25}$ and V$_{30}$, respectively). The highest D$_{98\%}$ value was obtained for beam setup 3 (2865.8 ± 106.7cGy) and it was statistically significant with respect to the other plans ($P < 0.01$). D$_{2\%}$ values obtained were quite similar for all beam setups, so their differences were not statistically significant ($P > 0.73$).

HI value obtained using beam setup 3 (0.12 ± 0.03) was also significant with respect to the other beam setups ($P < 0.01$). On the contrary, CF between beam setup 3 and beam setup 4 was not statistically significant ($P = 0.63$). Beam setup 3 and beam setup 4 CF were significant with respect to beam setup 1 and beam setup 2, respectively ($P < 0.04$). Table 4 shows that beam setup 1 has a slightly higher value of V$_{25}$ and the

same HI when compared to beam setup 4. Hence, beam setup 4 was chosen as the second-best beam setup in terms of V_{25} and HI, although the results were not significant ($P > 0.7$). $D_{2\%}$ was significantly reduced compared to RTOG 0933 criteria (37.5 Gy), which is of clinical relevance due to the hot spots reduction within the brain.

Hippocampi $D_{100\%}$ average value was under RTOG 0933 recommendations (9 Gy). Beam setup 2 achieved the lowest values, being significantly different than beam setups 1 and 4 results ($P < 0.03$), but not with respect to results yielded by beam setup 3 ($P = 0.77$). Maximum doses to the hippocampus obtained from the four investigated beam setups were all below 16 Gy, in accordance with the RTOG 0933 recommendations. A significant difference was obtained when comparing beam setups 1 and 2 ($P = 0.02$), and beam setup 2 being the one achieving the lowest values. Figure 2 depicts color wash isodoses of the same CT slice for the same patient and different beam setups used. A representative slice for the hippocampal avoidance process has been selected to illustrate the steep gradient achieved by all beam arrangements investigated. Overall, beam setup 3 (bottom left) was able to produce the best dose gradient between the hippocampi and PTV_{eval}, as the regions surrounding hippocampal avoidance structures were better covered.

In terms of eyes and lenses doses, the lowest D_{max} values were achieved utilizing beam setup 2 whereas the highest D_{max} values were obtained with beam setup 1 [Table 5]. In both
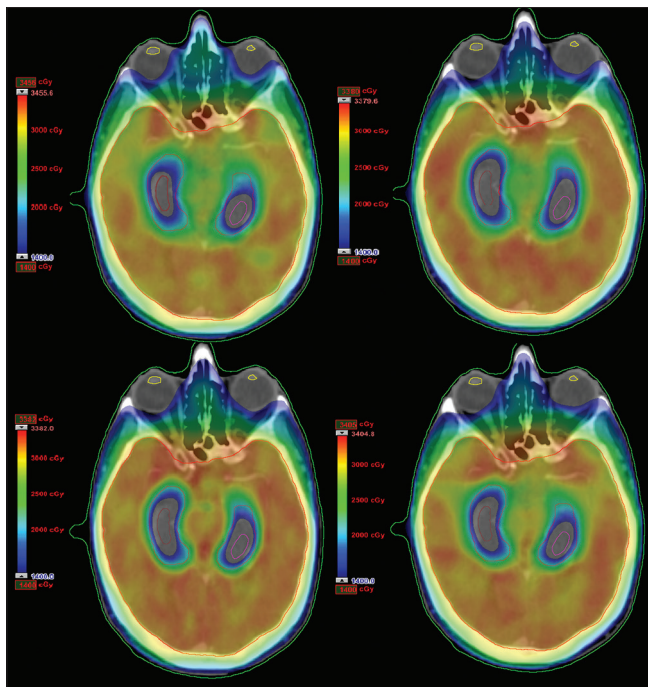
Figure 2: Color wash isodoses for a representative patient and optimized by using the four distinct beam arrangements utilized in this study. Color wash range was set between maximum dose and 14 Gy to illustrate the steep gradient associated with the hippocampal avoidance process. Beam setups 1 (top left), 2 (top right), 3 (bottom left), and 4 (bottom right) results are depicted

cases, the discrepancies were significant when comparing beam setup 2 with beam setup 1 for eyes ($P < 0.01$) and with setup 4 for lenses ($P < 0.03$). For brainstem, chiasm and optic nerves, no statistical significance was found among all four setups ($P > 0.27$).

The analysis of MU and treatment time indicated that beam setup 1 delivered the lowest number of MU (680 ± 38) in the shortest time (2.51 ± 0.32 min), mainly due to the reduced number of arcs and the absence of couch angles different from $0°$. Considering MU only, beam setup 1 results were statistically significant with respect to beam setups 3 and 4 ($P \ll 0.01$), but not with respect to beam setup 2 ($P = 0.3$). Regarding treatment time, beam setup 1 results were significant with respect to the other beam setups ($P \ll 0.01$).

The assessment of the PTV_{eval} dose coverage showed that beam setup 3 was the best. The dose distributions obtained for this arrangement were the most homogeneous (lowest HI) and conformed to the target (highest CF). Hippocampi, eyes and lenses were spared, achieving the second-best results (for D_{max} values). The best results for hippocampal sparing, as well as for lenses sparing, were obtained using beam setup 2. Beam setup 3 had a major cost of MU alongside with beam setup 4, while it performed faster than beam setups 2 and 4. The lowest treatment time and number of delivered MU were obtained with beam setup 1. The latter has the strength of being the fastest in overall treatment time. Moreover, two coplanar arcs have the benefit of reducing the probability of operating errors owing to the lack of couch angles distinct from $0°$.

Three out of four beam arrangements evaluated in the present study are similar to those appearing in other publications. A brief comparison between our results and those publications' results is addressed below. Beam setup 2 is similar to that employed in Krayenbuehl *et al.*[24] In this study, the authors obtained higher values of PTV_{eval} V_{30}, $D_{2\%}$, and HI (92%, 33.6 Gy and 0.24, respectively). In addition, PTV_{eval} $D_{98\%}$ and hippocampus D_{max} and $D_{100\%}$ were lower than our results (25.8 Gy, 8.1 Gy, and 14.1 Gy, respectively). Beam setup 3 is similar to the one utilized by Tsai *et al.*[25] They obtained a lower PTV_{eval} V_{30} (85%) and a lower hippocampus $D_{100\%}$ (8 Gy). A higher PTV_{eval} $D_{2\%}$ (33.6 Gy) and a higher hippocampus D_{max} (15 Gy) were found. Beam setup 4 is employed in one of the cases studied in Lee *et al.*[27] In this study, PTV_{eval} $D_{2\%}$ was similar to our result, although V_{30} was lower than 90%. Higher hippocampus D_{max} (20.1 Gy) and $D_{100\%}$ (10 Gy) were also found.

CONCLUSIONS

From the preliminary study carried out in seven patients, it can be shown that the decrement in hippocampal dose was greater from PTV5 to PTV7 than from PTV7 to PTV9 for all beam setups. For distances lower than 7 mm, there was little reduction in PTV_{eval} coverage for all beam setups. Hence, PTV7 was chosen to be the preferred optimization structure to achieve a low hippocampi dose while maintaining a reasonable PTV_{eval} coverage.

Regarding the beam setup comparison, the performance of four distinct VMAT beam arrangements for HS-WBRT was assessed in 20 patients. In all cases, the RTOG 0933 dose criteria were achieved, not incurring any unacceptable variation. Beam setup 3 was the best in terms of PTV_{eval} coverage, HI, and CF while being the second best at sparing hippocampi and lenses. Considering treatment time, beam setup 3 was the second-fastest beam arrangement but it delivered the highest number of MU. On the contrary, beam setup 1 was the fastest treatment and it delivered the least number of MU. Furthermore, this beam setup offers a higher robustness because of the absence of couch angles distinct from 0°.

The optimum selection among the investigated beam arrangements might depend on the need for PTV_{eval} coverage or hippocampal sparing, and the workload of patients at the specific institution. To reduce the amount of time dedicated to treatment planning, and to facilitate automation, the optimization parameters (such as weights, objectives, or constraints) may be stored as templates. For this purpose, patient positioning should be reproducible and optimized to achieve the desired objectives automatically. Moreover, a proper hippocampal contouring is essential if benefits are to be obtained. All the VMAT beam setups investigated in our study entail a good approximation to HS-WBRT because they provide the steep dose gradient required between avoidance regions and target tissue, a high degree of target conformity and quite acceptable homogeneity and target coverage. However, we consider that beam setup 3 seems to entail the most interesting balance between OAR sparing, PTV_{eval} coverage, and delivery time.

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Conflicts of interest
There are no conflicts of interest.

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