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Dosimetric evaluation of a hybrid treatment planning for whole-brain radiation with hippocampal sparing

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► ***Original article***

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ABSTRACT

Background*:** To study the possible dosimetric benefits of a Hybrid planning technique that consists of combining intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) for whole brain radiation therapy hippocampal-sparing (WBRT-HS). ***Materials and Methods*:** Three types of plans were made for 15 patients, namely Hybrid, pure IMRT, and pure VMAT and retrospectively compared. Each plan was made using contoured structures on computed tomographic (CT) images fused with magnetic resonance imaging (MRI). The homogeneity (HI) and conformity (CI) indices of the planning target volumes (PTVs) were calculated to establish the dosimetric quality in all plans. The dose received to organs at risk (OARs), number of monitor units (MUs) and treatment time were evaluated for each type of planning technique. ***Results: Hybrid plans showed superior homogeneity ($p = 0.04$) and conformity ($p = 0.01$) indices compared to IMRT and VMAT plans. In terms of hippocampus sparing, the Hybrid technique showed almost equal D100% and maximum dose (Dmax) values compared to the other techniques, but without statistical significance ($p > 0.05$); however, there was a significant difference for the left hippocampus, where the IMRT technique obtained the best result ($p < 0.001$). Hybrid plan values for dose delivered to the remaining OARs, MUs and treatment times were intermediate between those of IMRT and VMAT. ***Conclusion:*** Compared to the IMRT and VMAT plans, the hybrid plan showed improved dosimetric plan quality along with intermediate dose values to the OARs.

INTRODUCTION

Brain metastases will occur in 30% of patients with some type of neoplasia [1]. Whole brain radiation therapy (WBRT) is commonly used in patients with this condition [2]. Unfortunately, WBRT has been reported to cause long-term adverse neurological effects, such as leukoencephalopathy, cognitive deterioration, cerebellar dysfunction, and dementia [3–5]. These effects are progressive and irreversible. The evidence also shows that WBRT leads to deterioration in some cognitive functions such as learning, memory and spatial orientation [6, 7]. There is strong evidence to suggest that damage to the hippocampus results in neurocognitive impairment [8]. In a study by Abayomi [9], the hippocampus and surrounding medial temporal lobe cortex were identified as the critical area where radiation generates neurocognitive decline. It is possible that the high radiation sensitivity of the progenitor neural cells located in the dentate gyrus of the hippocampus is the reason for the previously described affections [10, 11]. Therefore, it is suggested that WBRT with sparing of hippocampi (WBRT-HS) may be an effective treatment option for most patients with brain metastases, in order to minimize any possible cognitive decline.

Radiation Therapy Oncology Group (RTOG) protocol 0933 is a phase II study where the use of hippocampal sparing during WBRT for the treatment of brain metastases was investigated [12]. Performing WBRT-HS requires complex treatment planning and the first studies in this area were made using helical tomotherapy [13–15] or linear accelerators based techniques, such as intensity modulated radiotherapy (IMRT) [11, 16] and volumetric modulated arc therapy (VMAT) [2, 17, 18]. There are several studies where dosimetric analysis for protection of the hippocampus are compared using different treatment techniques; Gondi *et al.* [15] compared helical tomotherapy with IMRT in terms of coverage to planning target volume (PTV), dose reduction to hippocampus and homogeneity, while Lee et al [19] did something similar but comparing IMRT versus VMAT. There are even studies where the three techniques are compared simultaneously [20]. Furthermore, it is possible to combine two techniques to build what is known as a "Hybrid plan" [21–23] which benefits from the advantages of the planning techniques that compose it. There are

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various types of hybrid plans. In Hybrid VMAT (H-VMAT) plans, the majority of the dose is delivered using static fields in Three-dimensional conformal radiotherapy (3D-CRT), while the remaining dose is delivered with VMAT [24].

In other hybrid plans, the IMRT technique is combined with VMAT, seeking to combine the intensity modulation control of IMRT with the angular sampling of VMAT [25]. Different dose proportions are reported between the types of fields for the construction of hybrid plans. In general, one third of the dose is delivered through IMRT or VMAT fields, while the rest is done through static fields [26]. However, the optimal dose ratio between the various types of plans is still an open topic of research [27]. To the best of the authors' knowledge, the hybrid planning technique for WBRT-HS has never been implemented. It has also not been established what optimal dose ratio between the various planning techniques is adequate for the construction of a hybrid plan in WBRT-HS. Treatments with hybrid plans generally report better dosimetric quality (better target coverage and dose distribution) along with greater protection to organs at risk (OARs) [28]. For all of the above, the authors consider that the implementation of the Hybrid technique for WBRT-HS is of great relevance and novelty. The present study was designed to compare the Hybrid plan technique with plans made with pure IMRT and VMAT in terms of conformity, homogeneity, doses to OARs and treatment time. All of the described above will be done by evaluating the dosimetric differences between these three treatment modalities for WBRT-HS, following the RTOG 0933 criteria.

MATERIALS AND METHODS

Delineation of target volumes and OARs

Fifteen patients who had undergone computed tomography (CT) simulation of the brain for other radiation therapy planning were retrospectively selected. Patients were 6-83 years old, with a mean age of 45.5 years. The demographic characteristics of all patients are shown in table 1.

Table 1. Patient demographic information.

Patient characteristics	
Median Age (years)	45 (6-83)
Gender	9 Female: 6 Male
Diagnosis	Central nervous system (CNS) tumors

The CT simulation was performed with a single-energy 64 slice Siemens SOMATOM Definition AS VA44A scanner (Siemens Healthier, Germany). Patients were placed in a supine position for the simulation process using a thermoplastic mask. CT images were acquired with a 2.5 mm slice thickness extending from the vertex to clavicles without contrast. All Digital Imaging and Communications in Medicine (DICOM) 3D-CT image data sets were then transferred to the Eclipse Treatment Planning System (TPS) (v. 16.1, Varian Medical Systems; Palo Alto, CA, USA). Additionally, all patients had previously undergone brain magnetic resonance imaging (MRI). All MRI acquisitions were performed on a 3-T MRI scanner (MAGNETOM Skyra, Siemens, Erlangen Germany), including a volumetrically acquired T1 postcontrast sequence, as well as T2 and fluid-attenuated inversion recovery sequences. Then MRI scans were semi-automatically fused to the bony anatomy on the planning CT images using an Eclipse mutual information algorithm for contouring and planning. The whole brain volume (all brain parenchyma tissue to C1 or C2) was contoured on CT bone window as the clinical target volume (CTV). The hippocampus was delineated according to the RTOG 0933 protocol [12] and defined as one paired organ. Both hippocampi were contoured on axial images and focused on medial hypointense signal from lateral ventricle temporal horn in accordance with RTOG atlas definition. The hippocampal avoidance region or hippocampal Planning Risk Volume (PRV) was generated using a computer-automated 5 mm isotropic margin expansion of the contoured hippocampus. The PTV was defined as CTV plus 5 mm expansion excluding the hippocampal PRV. The lenses, eyes, optic nerves, chiasm and hippocampus were contoured as OARs. Delineation was assessed and approved by a single radiation oncologist and reviewed by a second senior radiation oncologist.

The RTOG 0933 protocol was followed, which establishes a dose prescription for the entire brain PTV of 30 Gy in 10 fractions. In the previously mentioned protocol, high dose gradients are allowed in the brain [29]; this is done in order to achieve a correct coverage of the PTV, as well as limit the dose to the hippocampi and other OARs. The specific dosimetric criteria for compliance with the RTOG 0933 protocol are listed in table 2. Although the protocol does not state them explicitly, the following dose restrictions were established: D_{max} <30 Gy, D_{max} <10 Gy and mean dose (D_{mean}) <35 Gy for eyes, lenses and cochlea, respectively.

Table 2. RTOG 0933 dosimetric compliance criteria for hippocampal sparing (HS); $D_{2\%}$= Dose received by hottest 2% of PTV; $D_{98\%}$= Dose received by 98% of PTV; $D_{100\%}$= Dose received by 100% of hippocampus; D_{max}= maximum dose; V_{30Gy} = Volume of PTV that receives a 30 Gy dose.

Organ	Dose constraints	Acceptable variation
Whole brain PTV	$D_{2\%} \leq$ 37.5 Gy $D_{98\%} \geq$ 25 Gy $V_{30Gy} \geq$ 95%	$D_{2\%} \leq$ 37.5 to 40 Gy $D_{98\%}$ > 22.5 to 25 Gy $V_{30Gy} \geq$ 90% to 95%
Hippocampi	$D_{100\%} \leq$ 9 Gy $D_{max} \leq$ 16 Gy	$D_{100\%} \leq$ 9 to 10 Gy $D_{max} \leq$ 16 to 17 Gy
Optic Nerves	$D_{max} \leq$ 30 Gy	$D_{max} \leq$ 30 to 37.5 Gy
Chiasm	$D_{max} \leq$ 30 Gy	$D_{max} \leq$ 30 to 37.5 Gy

Planning techniques

The same medical physicist created an IMRT,

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VMAT, and Hybrid plan for each patient on the same CT fused with its corresponding MRI study. The goal was that 100% of the prescription dose should be delivered to at least 90% of the volume of the PTV for all plans. To make a fair comparison between the three types of techniques, all plans were normalized to this dose-volume point value. The dose delivered to the hippocampi and other OARs was reduced as much as possible. Treatment plans were generated by the Eclipse TPS with the AAA (anisotropic analytical algorithm) on a Varian VitalBeam Linear Accelerator (Varian Medical Systems, Palo Alto, CA) equipped with a 120 leaf multi-leaf collimator (MLC), using 6 MV beams, with a dose grid size of 0.25 cm.

For IMRT plans, 11 fields were used in total, five were coplanar (couch angle set to 0°) and six were in a different plane (i.e. a different couch angle). The coplanar fields were separated by 72°, the gantry angles were 0°, 72°, 144°, 216° and 288°. The couch angle was set to 90° for the remaining gantry angles, which were 181°, 223°, 265°, 307°, 332° and 30°. A collimator angle of 0° was chosen for all fields in order to reduce the dose to the OARs [30]. All fields had a 6 MV voltage. The sliding window modality with a stable dose rate of 600 monitor units (MUs)/ minute was maintained in all plans. Similar optimization priorities were set in the optimization algorithm. Achieving adequate coverage for the PTV was considered the most important, followed by limiting the dose to the hippocampi and to the rest of the OARs. The field arrangement for the IMRT plans can be seen in figure 1 (a).

The same voltage and dose rate were used for plans made with VMAT as with IMRT. For each patient, eight arc fields were used in total, four coplanar (couch angle set to 0°, with a gantry extension of 358°) and four in a different plane (couch angle set to 90°, with a gantry extension of 209°). Two of the coplanar fields were placed from 179° to 181 ° (anti-clockwise) and the remaining two from 181° to 179° (clockwise). Similarly, two of the fields with a couch angle of 90° were placed from 30° to 181° (counter-clockwise) and the other two from 181° to 30° (clockwise). For coplanar fields, two avoidance sectors were used in order to prevent direct entry of the beams through the eyes. For the anti-clockwise fields, the avoidance sector was 50° to 350° and for the clockwise fields it was 350° to 50°. To limit the Tongue-and-Groove effect [31], collimator angles of 10° and 350° were chosen for the clockwise and counterclockwise fields, respectively. A field size of 15 cm was used, since it is recommended to allow the MLC to obtain a better coverage of the target [32]. However, because all PTVs had dimensions greater than 15 cm, it was necessary to use four VMAT fields for each couch orientation. To make a fair comparison, the template and optimization goals were the same as in the IMRT plan. The field arrangement for the VMAT plans can be seen in figure 1 (b).

Hybrid plans were made by combining IMRT's 11-field plans and VMAT's eight-arc plans in a sum of plans between IMRT and VMAT plans. A dose proportion where 70% of the dose corresponded to the IMRT plan and 30% to the VMAT plan was chosen. This dose ratio was reported by Akbas *et al.* [22] and had the best dosimetric results overall. The original 11 IMRT fields and the eight VMAT fields were not changed. The dosimetric results of the Hybrid plans were evaluated in the plan sum. The field arrangement for the Hybrid plans can be seen in figure 1 (c).

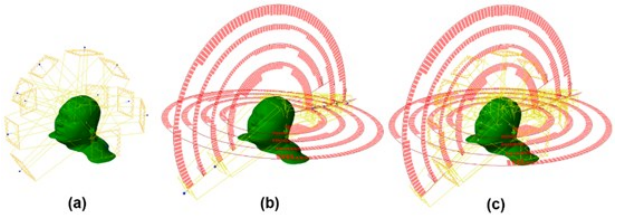

Figure 1. Field arrangement for a single patient: **(a)** IMRT, **(b)** VMAT and **(c)** Hybrid techniques.

Dosimetric evaluation

A dose-volume histogram (DVH) was created for the dosimetric analysis. The homogeneity index (HI) was calculated using equation 1 [33]:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (1)$$

Where $D_{2\%}$, $D_{98\%}$ and $D_{50\%}$ represent the doses received by 2% (near maximum dose), 98% (near minimum dose), and 50% of PTV's volume, respectively. A homogeneity index value of 0 would indicate an ideal dose distribution.

The conformity index (CI) was also calculated equation 2 [21]:

$$CI = \frac{V_{PTV,ref}}{V_{PTV}} \times \frac{V_{PTV,ref}}{V_{ref}} \quad (2)$$

Where $V_{PTV,\,ref}$ refers to the volume of the 100% of the prescribed dose that covers the PTV, V_{PTV} refers to the volume of the PTV, and V_{ref} is the volume of the 100% prescribing dose curve. A CI value of 1 indicates a perfect dose conformity. The treatment time in minutes was measured as the time interval in which the first to the last field was delivered including gantry rotation but not patient positioning. MUs were also recorded in all plans for comparison.

Statistical analysis

To analyze the dosimetric differences between the three planning techniques, the one-way Analysis of Variance (ANOVA) was used. When a significant difference was found ($p < 0.05$), the difference between each of these three types of plans for each effect was further investigated using the unpaired *t-test*. The statistical analyses were performed using the OriginPro Software Version 2018 (OriginLab Corporation, Northampton, MA, USA).

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RESULTS

The mean PTV volume was 1418.7 ± 196.29 cm^3. Treatment plans for all patients were in compliance with the RTOG 0933 protocol dosimetric criteria. Typical dose distributions at the hippocampi level are shown in figure 2; axial, coronal and sagittal views (from top to bottom) are shown for one representative patient.

Table 3 shows the mean values of HI, CI, $D_{100\%}$, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$, $D_{2\%}$, $D_{1\%}$, D_{mean} and D_{max} for the PTV, their standard deviations (SD) are also shown. The p-values with statistical significance between the three planning techniques are in bold format.

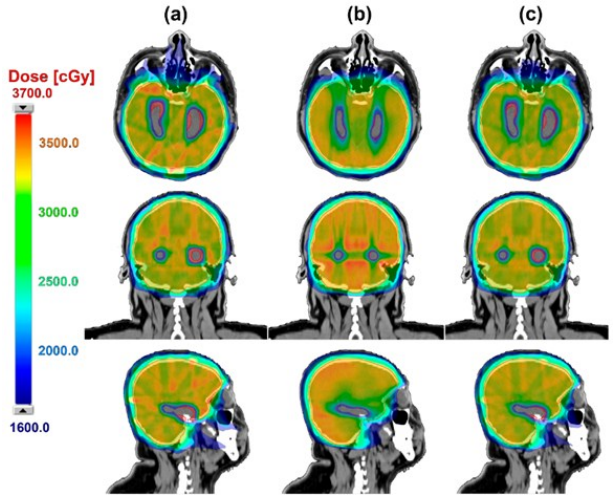

Figure 2. Dose distribution on axial, coronal, and sagittal views for one patient: **(a)** IMRT, **(b)** VMAT, and **(c)** Hybrid plan.

Table 3. PTV Dosimetric parameters for IMRT, VMAT and Hybrid plans; SD – standard deviation; HI – homogeneity index (equation 1); CI – conformity index (equation 2); bold p-values indicate statistical significance between the three planning techniques. All plans were normalized so that 90% of the PTV volume received a dose of 30 Gy.

Item	IMRT (mean ± SD)	VMAT (mean ± SD)	HYBRID (mean ± SD)	p-value
HI	0.2781 ± 0.0453	0.2862 ± 0.0331	0.2501 ± 0.0392	**0.04**
CI	0.8319 ± 0.0243	0.8268 ± 0.0212	0.8493 ± 0.0171	**0.01**
$D_{100\%}$ (cGy)	981.6 ± 74.55	1433.30 ± 134.71	1176.47 ± 71.88	**<0.001**
$D_{98\%}$ (cGy)	2463.83 ± 117.95	2494.12 ± 86.97	2481.76 ± 106.73	0.73
$D_{95\%}$ (cGy)	2940.63 ± 16.15	2785.36 ± 44.86	2887.03 ± 26.94	**<0.001**
$D_{50\%}$ (cGy)	3114.13 ± 11.90	3239.33 ± 41.94	3119.39 ± 31.41	**<0.001**
$D_{2\%}$ (cGy)	3330.22 ± 35.59	3422.49 ± 61.47	3262.1 ± 26.55	**<0.001**
$D_{1\%}$ (cGy)	3374.71 ± 40.29	3455.66 ± 63.03	3287.08 ± 31.22	**<0.001**
D_{mean} (cGy)	3093.61 ± 10.28	3189.72 ± 32.97	3082.55 ± 13.18	**<0.001**
D_{max} (cGy)	3836.24 ± 223.91	3686.39 ± 84.32	3524.77 ± 98.43	**<0.001**

The average HI value for the IMRT technique was 0.2781 ± 0.0453, for the VMAT plan it was 0.2862 ± 0.0331 and for the Hybrid plan it was 0.2501 ± 0.0392 (p = 0.04). The mean CI value for the IMRT technique was 0.8319 ± 0.0243, for the VMAT technique it was 0.8268 ± 0.0212 and for the Hybrid plan it was 0.8493±0.0171 (p=0.01). There were significant differences for both quality indices when comparing the three types of plans. The indices belonging to the Hybrid plan obtained the best results. For $D_{100\%}$, $D_{50\%}$ and D_{mean} the VMAT technique had the highest dose values (p <0.001); for $D_{98\%}$, the VMAT technique also showed the highest dose value but there was no significant difference between the three planning techniques (p = 0.73). The IMRT plan had highest dose value for $D_{95\%}$ (p <0.001). The high doses values ($D_{2\%}$, $D_{1\%}$ and D_{max}) for the Hybrid technique were the smallest among the three types of plans (p<0.001).

The dosimetric comparisons of the hippocampi and the rest of OAR are shown in table 4. The p-values with statistical significance are again in bold format. In terms of hippocampus avoidance, the Hybrid technique had a very similar $D_{100\%}$ values compared to the other two types of plan. Plans made with VMAT had the lowest value, but without statistical significance (p> 0.05, for both hippocampi). Similarly, for the D_{max} delivered to the right hippocampus, the three types of plans had similar dose values without showing a significant difference (p = 0.10). However, for the left hippocampus there was a statistically significant difference in D_{max}, being the IMRT technique the one that obtained the lowest value (D_{max}=1327.81 cGy, p<0.001). In both optic nerves, the VMAT technique showed the lowest D_{max} values (p = 0.02). For the chiasm, the Hybrid plan had the smallest D_{max}, however there was not a significant statistical difference (p = 0.18). For lenses, eyes and cochlea, OARs not specifically mentioned in the RTOG 0933 protocol, the hybrid technique obtained intermediate D_{max} and D_{mean} values compared to IMRT and VMAT. The average DVHs of PTV and OARs are shown in figure 3.

The MUs and treatment time of the three planning techniques are shown in table 5. The p-values with statistical significance are in bold format. The MUs and treatment time values for the Hybrid plans were between those of the IMRT and VMAT plans.

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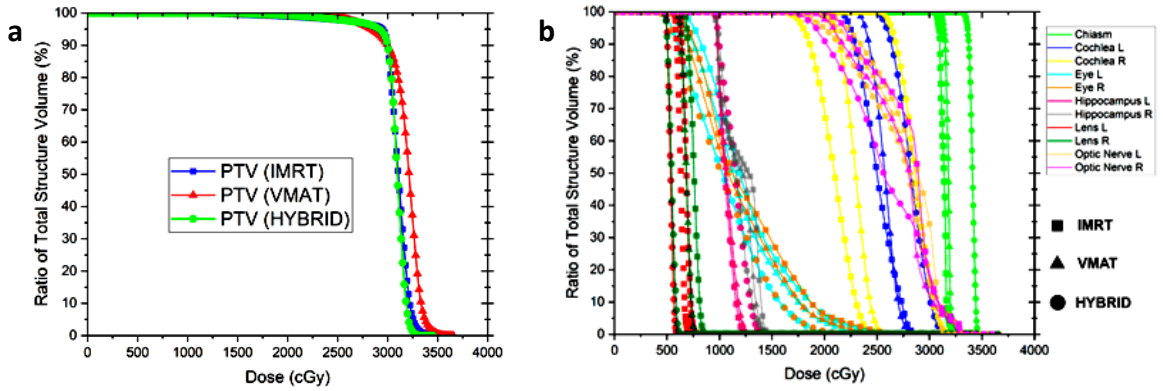

Figure 3. Representative Dose-Volume Histograms of target volumes **(a)** and OARs **(b)**. All plans were normalized so that 90% of the PTV volume received a dose of 30 Gy.

Table 4. OARs Dosimetric parameters for IMRT, VMAT and Hybrid plans; SD – standard deviation; bold p-values indicate statistical significance between the three planning techniques.

Organ	Parameter	IMRT (mean ± SD)	VMAT (mean ± SD)	HYBRID (mean ± SD)	p-value
Chiasm	D_{max}(cGy)	3253.23 ± 126.03	3207.30 ± 152.56	3165.17 ± 101.78	0.18
Cochlea Left	D_{mean} (cGy)	2772.99 ± 614.78	2871.56 ± 322.26	2756.01 ± 447.72	0.08
Cochlea Right	D_{mean} (cGy)	2454.01 ± 644.21	2962.48 ± 251.44	2541.09 ± 427.27	**0.01**
Eye Left	D_{max} (cGy)	2199.33 ± 585.92	1765.05 ± 345.39	1994.73 ± 487.63	0.06
Eye Right	D_{max} (cGy)	2340.11 ± 572.98	1883.55 ± 372.52	2119.12 ± 497.38	**0.04**
Hippocampus Left	$D_{100\%}$ (cGy)	977.64 ± 22.39	955.49 ± 33.83	975.41± 29.40	0.08
	D_{max} (cGy)	1327.81 ± 62.69	1608.68 ± 61.91	1404.77 ±60.44	**<0.001**
Hippocampus Right	$D_{100\%}$ (cGy	959.83 ± 30.59	948.60 ± 22.22	965.27 ± 13.92	0.15
	D_{max} (cGy)	1549.24 ± 57.88	1598.21±75.17	1570.84 ± 48	0.10
Lens Left	D_{max} (cGy)	780.36 ±110.57	543.82 ± 55.31	691.53 ± 91.68	**<0.001**
Lens Right	D_{max} (cGy)	779.89 ± 113.96	548.05 ± 54.55	694.48 ± 93.34	**<0.001**
Optic Nerve Left	D_{max} (cGy)	3362.26 ± 296.07	2975.86± 350.56	3097.14 ± 202.82	**0.002**
Optic Nerve Right	D_{max} (cGy)	3364.61 ± 270.74	3006.02 ± 312.79	3113.76 ± 178	**0.002**

Table 5. MU values and delivery time of treatment for IMRT, VMAT and Hybrid plans; SD – standard deviation; bold p-values indicate statistical significance between the three planning techniques.

Parameters	IMRT (mean ± SD)	VMAT (mean ± SD)	HYBRID (mean ± SD)	p-value
MUs	3532.23 ± 289.65	770.79 ± 55.24	2596.20 ± 120.30	**<0.001**
Time (min)	9.72 ± 0.41	6.23 ± 0.34	7.20 ± 0.36	**<0.001**

DISCUSSION

Recent evidence suggests that whole brain radiation is associated with a deterioration of cognitive function [34, 35]. Hippocampal dose avoidance is a way to reduce neurocognitive toxicity, this has been achieved through the use of advanced planning techniques, such as IMRT and helical tomotherapy [12, 15, 36]. The modern planning methods have allowed a correct implementation of the WBRT-HS while having adequate coverage of the PTV and there are dosimetric studies where the results obtained between them are compared [37]. Gondi *et al.* [15] compared the efficiency of helical tomotherapy with IMRT, and found both techniques suitable for WBRT-HS. There are even studies such as the one by Saad *et al.* [38] where the dosimetric differences between IMRT and VMAT are compared for WBRT-HS. They concluded that the VMAT technique showed better results in the CI and HI indices, with lower mean and maximum dose values delivered to the hippocampi compared to IMRT. There are multiple reports in literature where it is confirmed that both techniques are suitable for WBRT-HS [18, 39, 40]. Despite all of the above, there is the possibility that neither of them is sufficient to meet certain dosimetric criteria. For this reason, Earl et al [41] proposed a hybrid treatment scheme combining the virtues of IMRT and VMAT. Matuszak *et al.* [42] proposed an IMRT/VMAT hybrid optimization strategy where IMRT intensity modulation was combined with single VMAT arches, this was applied in patients with prostate, pancreas and brain cancer. The importance of the approach of a Hybrid planning technique lies in the fact that both IMRT and VMAT have marked advantages and disadvantages. The IMRT technique is associated with the delivery of a large number of MU's, and therefore longer treatment times[43]. While the VMAT planning process turns out to be longer and more complex than in IMRT, and sometimes resulting in plans with lower dosimetric quality [44]. In the present work, a Hybrid planning technique based on the combination of IMRT and VMAT for WBRT-HS was proposed. The plans made with the Hybrid technique showed a superior irradiation homogeneity, conformity and lower maximum doses to the target volume. The hybrid plan meets the criteria of the RTOG 0933

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protocol and also presents adequate dose values for cochleae, lenses and eyes, OARs not explicitly mentioned in said protocol. The clinical importance of this is that an improvement in conformity and homogeneity for the PTV decreases the possibility of local recurrence and cognitive impairment [11, 12, 14–17, 19, 20, 29, 37, 45, 46].

There are several studies in the literature where a Hybrid technique is applied to various regions of the body. For nasopharyngeal cancer, Zhao *et al.* [44] made a dosimetric comparison between plans made with nine fields of IMRT and double arch VMAT with Hybrid IMRT/VMAT plans. Their Hybrid plan was generated with seven IMRT fields and a single VMAT arc and showed better conformity and homogeneity compared to the pure IMRT and VMAT plans along with lower doses to the temporomandibular joints, temporal lobes and mandible. They also reported fewer MUs compared to IMRT plans and lower doses to OARs such as parotids, brainstem and spinal cord compared to plans made in VMAT. For patients with early stage left breast cancer, Chen *et al.* [47] devised different types of Hybrid plans composed different combinations of IMRT, VMAT and 3D-CRT fields. In their work, the Hybrid plans obtained better conformity indices, and lower dose values for the following parameters: heart volume that received 5 Gy (V_{5Gy}), $D_{2\%}$ to the left ventricle, and volume of normal tissue that received 50.4 Gy ($V_{50.4Gy}$). Hybrid plans have also been made in cases of pelvic tumors. For 10 patients with prostate cancer Ozturk *et al.* [23] created a Hybrid plan where 50% of the prescription dose was delivered in IMRT and the remaining 50% in VMAT. They reported lower values in comparison to pure IMRT and VMAT for the volume of bladder and rectum irradiated to 50 Gy (V_{50Gy}), as well as a reduction in the mean dose to femoral heads. They also reported an improvement in dose homogeneity for the PTV. The results described above are similar to those obtained in this work (See tables 3 and 4). This shows the potential benefit of implementing a Hybrid plan, since all these benefits could be obtained without compromising the coverage to the target volume, while obtaining a plan with a better dosimetric quality.

The dosimetric superiority of the Hybrid plan lies in the fact that it exploits the advantages of both the IMRT and VMAT techniques. The IMRT technique in general produces plans with better homogeneity compared to those of VMAT, this is due to its better beam modulation. On the other hand, the VMAT technique has a superior angular sampling which favors the correct conformation to the target volume. However, none of them (beam modulation and angular sampling) is sufficient alone to obtain an appropriate dose distribution. For all of the above, the authors suggest that the use of the Hybrid technique can be considered as a dosimetric improvement for WBRT-HS compared to only IMRT and VMAT; since it includes the advantages of both techniques while meeting the criteria of the RTOG 0933 protocol. Two factors explain the intermediate values compared to the other techniques for the MUs and the treatment time: the complexity of the sequence of movements of the MLC for its IMRT component and the average aperture of the optimized field size for the VMAT component. A greater depth of explanation was applied to cervical cancer by Martín-Tovar *et al.* [48] in a previous work.

Finally, it is important to mention that there are various research topics where knowledge about Hybrid plans could be deepened. To mention a few, the optimum ratio between IMRT and VMAT components has not yet been established. Studies such as those by Zhao *et al.* [44] proposed a 2:1 ratio for IMRT and VMAT dose components. However, works such as Balaji *et al.* [49] and Bedford *et al.* [50] suggest other proportions. In this work, an IMRT/VMAT ratio of 7:3 was established. This suggests that there are various ways to implement and develop a Hybrid plan.

CONCLUSIONS

The combination in a Hybrid plan of the IMRT and VMAT techniques resulted in a plan with better dosimetric quality compared to plans made only with IMRT and VMAT. It also allows meeting the dose requirements for Hippocampi and other OARs described in the RTOG 0933 protocol, as well as for other organs not included in said protocol. The Hybrid planning technique is a viable option for whole brain radiotherapy with protection to hippocampi.

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Consent for publication: All authors involved consent to publish work here within

Ethical approval: This research work complies with the considerations issued in the Nuremberg Code, the Declaration of Helsinki promulgated in 1964 and its various modifications, including the update of Fortaleza, Brazil in 2013, as well as the international guidelines for medical research with human beings adopted by WHO and the Council for International Organizations for Research with Human Beings; In Mexico, it complies with the provisions of the General Health Law and the INAI (Instituto Nacional de

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Transparencia, Acceso a la Información y Protección de Datos Personales) on Research for Health and Protection of Personal Data, respectively. This work was done according to ethical code no: F-2023-3203-040, date 05/12/2023.

***Author contribution*:** E.A.M.T. conceived and designed the study, created all treatment plans, and drafted the final manuscript. A.H.B.A. and J.L.G.S., designed the inclusion criteria, reviewed the patient database for patient selection, delineated all OARs and PTVs and clinically evaluated all treatment plans. L.E.C.P. performed the statistical analysis and designed all figures in the manuscript. All authors read and approved the final manuscript.

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