



Modulated Arc Therapy for hippocampal-avoidance whole brain radiation therapy: planning comparison with intensity modulated Radiation Therapy

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Abstract

This study aimed to evaluate the modulated arc therapy (mARC) technique as a planning and treatment option for hippocampal sparing whole brain radiotherapy (HS-WBRT) following the Radiation Therapy Oncology Group (RTOG) 0933 dosimetric criteria. Computed tomography (CT) and magnetic resonance imaging (MRI) were selected retrospectively for 15 patients. Two types of plans were created for each patient, namely an intensity-modulated radiation therapy (IMRT) and a mARC plan. IMRT and mARC plans were compared in terms of plan quality indices, absorbed dose to organs at risk (OARs), number of monitor units (MUs), and treatment time. All plans in both techniques were considered clinically acceptable for treatment. However, IMRT plans presented a higher conformity ($p=0.01$) as well as a higher homogeneity as compared to mARC plans, but this difference was not statistically significant ($p>0.05$). In terms of the preservation of the hippocampus, it was observed that the IMRT plans achieved significantly lower doses for both 100% of its volume and for its maximum dose ($p<0.001$). The evaluation of the remaining OARs showed that the IMRT technique resulted in lower doses, and significant differences were observed for the following organs: left cochlea ($p<0.001$), left eye ($p<0.001$), right eye ($p=0.03$), both lenses of the eye ($p<0.001$), and right optic nerve ($p=0.02$). Despite these differences, the absolute differences in all dosimetric parameters were low enough to bear any clinical relevance. A drastic (close to 65%) and significant ($p<0.001$) decrease was observed in the number of MUs for the mARC plans. This resulted in a substantial decrease in treatment time (60.45%, $p<0.001$). It is concluded that the mARC technique is a feasible planning and treatment solution for HS-WBRT that meets the RTOG 0933 criteria. The main advantage of using mARC over IMRT for HS-WBRT is the considerable reduction in MUs and treatment time.

Keywords Whole brain radiotherapy · Hippocampal sparing · Modulated arc (mARC) technique · Brain metastases · Hippocampus

Introduction

Brain metastases occur in 20–40% of cancer patients with poor prognosis (Chabot et al. 2017; Mn et al. 2018). Whole brain radiotherapy (WBRT) is a fundamental treatment option for these patients as it offers control over visible

tumours and non-visible metastases while improving quality of life (Aoyama et al. 2007, 2023). However, WBRT has been reported to cause irreversible neurological effects, such as leukoencephalopathy (Mayinger et al. 2020), cognitive deterioration (Roman and Sperduto 1995), cerebellar dysfunction (Eekers et al. 2018), and dementia (Brown et al. 2007). Some cognitive functions are also affected by WBRT such as learning, memory and spatial orientation (Crossen et al. 1994; Warrington et al. 2012). There is strong evidence that these neurocognitive impairments are correlated to effects on the limbic system, especially the hippocampus (Ghia et al. 2007; Truc et al. 2013). Some clinical studies hypothesize that radiation-induced damage to progenitor neuronal cells in the subgranular zone of the hippocampus

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is related to the previously described impairment (Nagai et al. 2000; Siglin et al. 2014). Therefore, and in order to minimize possible neurocognitive impairment, hippocampal sparing whole brain radiotherapy (HS-WBRT) is proposed as a treatment option for patients with brain metastases.

HS-WBRT has recently been evaluated in a prospective phase II study by the Radiation Therapy Oncology Group (RTOG; RTOG 0933) (Gondi et al. 2014). Contouring and planning for HS-WBRT is generally difficult, however, due to the central location of the hippocampus in the brain (Lin et al. 2020). Previous studies have reported the feasibility of delivering HS-WBRT with various treatment techniques such as helical tomotherapy (Gondi et al. 2010b; Brodin et al. 2014), intensity-modulated radiotherapy (IMRT) (Siglin et al. 2014; Moon et al. 2016) and volumetric modulated arc therapy (VMAT) (Sood et al. 2017; Zhang et al. 2017).

Modulated arc therapy (mARC) is an intensity-modulated hybrid rotational irradiation technique, which delivers treatment in a “burst mode” (Sarkar et al. 2015). It emerges as an alternative to VMAT, where the dose is delivered continuously while the gantry and multi-leaf collimator (MLC) move, whereas in mARC dose delivery is carried out in small arcs, called arclets, during which the MLC has a fixed conformation, and this alternates with gaps where no radiation is emitted at the same time that the MLC leaves acquire the conformation of the next field (Bell et al. 2016b; Luna and De Torres Olombrada 2019). In both techniques the gantry is kept rotating continuously around the patient. Treatments in mARC have been found to have good dosimetric and technical performance for treatments in various anatomical sites (Dzierma et al. 2013, 2014a, b). Moreover, one of the advantages of mARC over VMAT is that it allows for better plan optimization since it is not necessary to irradiate an intermediate field configuration (Choi et al. 2018). A disadvantage of mARC over VMAT is the generally longer treatment time, attributed to the burst mode interrupting the MLC movement. However, this offers an additional degree of freedom to the configuration of the MLC. Another advantage is that in case of treatment interruption, the precise knowledge of the delivered dose at each instant is ensured (Dzierma et al. 2014b). In addition to the above, due to the continuous movement of the gantry, there is a significant reduction in treatment time compared to IMRT (Bell et al. 2016a).

A large number of prior studies have compared VMAT and IMRT for treatments where HS-WBRT is required (Wang et al. 2015, 2017; Gondhowiardjo et al. 2019; Jiang et al. 2019). However, to the best of the authors’ knowledge, mARC, which is technically different from VMAT, has not been systematically evaluated for such treatment or compared with other techniques. Consequently, in the present study, a dosimetric comparison is made between IMRT and

mARC planning techniques in order to verify their sparing ability to the hippocampus as well as to other organs at risk (OARs). The present study was designed to compare mARC plans with IMRT plans in terms of plan quality (conformity, homogeneity, doses to the OARs and treatment time). This was done by evaluating the dosimetric differences between these two treatment modalities for HS-WBRT, following the RTOG 0933 criteria (Mehta et al. 2011).

Materials and methods

Delineation of target volumes and organs at risk

Fifteen patients who had undergone computed tomography (CT) simulation of the brain for other radiation therapy planning were retrospectively selected. Patients were 6 to 83 years old, with a mean age of 45.5 years. The CT simulation was performed with a single-energy 64 slice Siemens SOMATOM Definition AS VA44A scanner (Siemens Healthineer, Germany). Patients were simulated in the supine position using a thermoplastic mask for immobilization. The original CT images were acquired with a 2.5 mm slice thickness extending from the vertex to clavicles without contrast. Subsequently, they were subjected to an image reconstruction process to acquire a final thickness of 1.25 mm, which is recommended by the RTOG 0933 protocol (Mehta et al. 2011). All 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), including a volumetrically acquired T1 postcontrast sequence, as well as T2 and fluid-attenuated inversion recovery sequences - all of them with an axial slice thickness of 1.25 mm. 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 (Gondi et al. 2014). Both hippocampi were contoured manually using 2D brush 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 (H-PRV) was generated using a computer-automated 5 mm isotropic margin expansion of the contoured hippocampus. The planning target volume (PTV) was defined as CTV expanded by 5 mm (excluding both H-PRVs) to allow for setup and inter- and intrafraction localization errors (Gondi et al. 2022). The lenses, eyes,

Fig. 1 Pseudo-structures for optimization (shown in magenta). E_1 and E_2 are shown in sagittal planes (upper images), while E_3 (lower image) is shown in an axial plane. Hippocampal Planning Risk Volumes (H-PRVs) are shown in blue and hippocampi in green

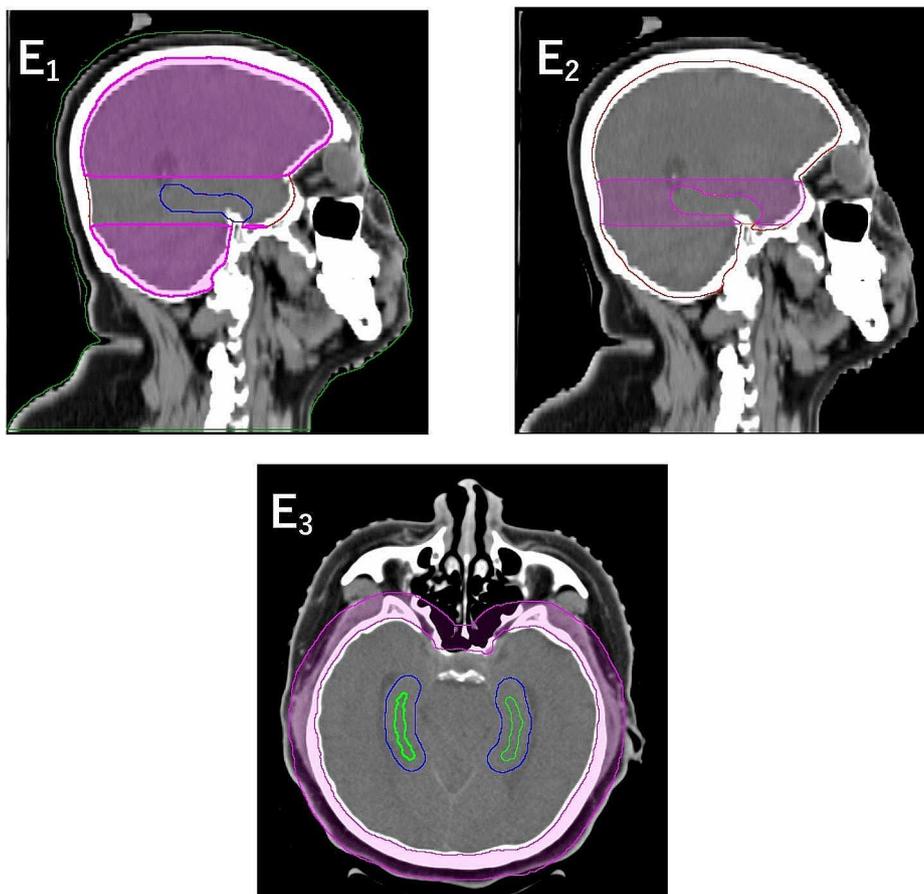


Table 1 RTOG 0933 dosimetric compliance criteria for hippocampal sparing (HS) (Mehta et al. 2011); $D_{2\%}$ - absorbed dose received by hottest 2% of planning target volume (PTV); $D_{98\%}$ - dose received by 98% of PTV; $D_{100\%}$ - dose received by 100% of hippocampus; D_{max} - maximum dose; V_{30Gy} - volume of PTV that receives a 30 Gy dose

Radiation Therapy Oncology Group 0933 guidelines		
Whole brain PTV	$D_{2\%} \leq 37.5$ Gy $D_{98\%} \geq 25$ Gy $V_{30Gy} \geq 95\%$	($D_{2\%} \leq 40$ Gy is allowed) ($D_{98\%} \geq 22.5$ Gy is allowed) ($V_{30Gy} \geq 90\%$ is allowed)
Hippocampi	$D_{100\%} \leq 9$ Gy $D_{max} \leq 16$ Gy	($D_{100\%} \leq 10$ Gy is allowed) ($D_{max} \leq 17$ Gy is allowed)
Optical nerves and optical chiasm	$D_{max} \leq 30$ Gy	($D_{max} \leq 37.5$ Gy is allowed)

optic nerves, chiasm, hippocampi, and cochleae were contoured as OARs. Delineation was assessed and approved by a single radiation oncologist and reviewed by a second senior radiation oncologist.

Pseudo-structures for optimization were also contoured for the planning process, in order to shape the dose within these regions. The pseudo-structures for optimization were as follows: the first structure (E_1) included the entire volume of the lower and upper portions of the PTV, beginning 1 or 2 CT slices after the H-PRV. The second structure (E_2) comprised the middle region of the PTV, obtained by subtracting

E_1 from the total PTV (without margins). Finally, the third structure (E_3) was a 1.5 cm ring surrounding the PTV. An example of these pseudo-structures for optimization for one patient is shown in Fig. 1.

The dose prescription to the whole brain PTV was set at 30 Gy in 10 fractions. The dosimetric criteria established in the RTOG 0933 protocol were followed. In this protocol, high doses are allowed in the PTV to achieve an adequate dose gradient and thus preserve the hippocampi (Krayenbuehl et al. 2017). The rest of the dosimetric criteria are shown in Table 1. Although the protocol does not state them explicitly, the following dose restrictions were established: maximum dose (D_{max}) < 30 Gy, D_{max} < 10 Gy and mean dose (D_{mean}) < 35 Gy for eyes, lenses and cochleae, respectively.

Planning techniques

The same medical physicist created an IMRT and a mARC plan for each patient. All plans were normalized to ensure that 100% of the prescription dose covered 90% of the PTV. It was also sought to reduce the dose to the hippocampi and other OARs as much as possible. Treatment plans were generated by the Eclipse TPS with the AAA (anisotropic analytical algorithm) on a Siemens Artiste linear accelerator with

Table 2 Beam arrangement for intensity-modulated radiation therapy (IMRT) plans

Beam	Gantry angle (°)	Collimator angle (°)	Couch angle (°)
1	30	40	320
2	310	340	330
3	180	90	45
4	104	25	10
5	49	28	16
6	9	0	276
7	265	350	330
8	317	340	16
9	319	90	270

Table 3 Beam arrangement for modulated arc therapy (mARC) treatment plans; CCW = counterclockwise; CW = clockwise

mARC fields	Field 1	Field 2	Field 3	Field 4
Collimator angle (°)	85	95	15	345
Gantry angle (°)	CCW 179.8-0	CCW 0-180.2	CW 180.2-0	CW 0-179.8
X1 Collimator Jaw (cm)	2-3	2-3	8-9	2-3
X2 Collimator Jaw (cm)	9-10	9-10	2-3	8-9
Y1 Collimator Jaw (cm)	9-10	9-10	7-9	7-9
Y2 Collimator Jaw (cm)	9-10	9-10	9-10	9-10

a 160 MLC (leaf width 5 mm at the isocenter), using 6 MV beams, with a dose grid size of 0.25 cm.

For IMRT plans, nine non-coplanar fields were used with a maximum of 100 segments (Andreas and Kundapur 2015) per beam in the step-and-shoot modality with a stable dose rate of 300 MUs/minute maintained in all plans. The geometric configuration of the treatment fields used was based on a previous study (Wang et al. 2017). Table 2 shows the parameter settings for each of the IMRT treatment fields. All treatment fields were positioned to adequately cover the entire surface of the target volume. The adequate coverage

of the PTV was the main priority in the optimization goals, followed by reducing the dose to the hippocampus and the rest of the OARs as much as possible. The field arrangement for the IMRT plans can be seen in Fig. 2 (a).

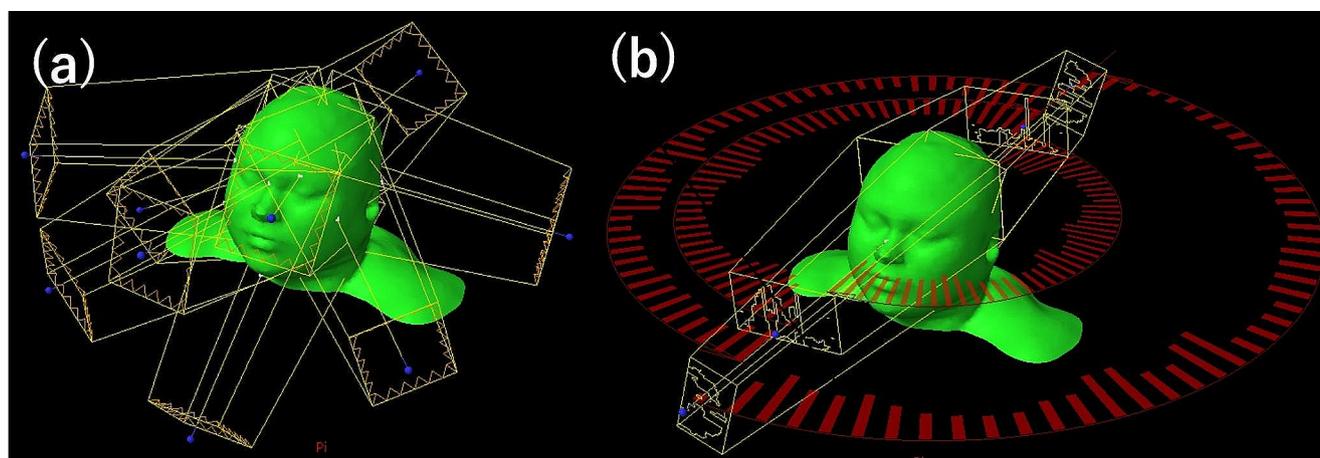
Beam arrangements for VMAT as described in (Yuen et al. 2020, 2022) were used to create four coplanar mARC fields. All fields had optimization points every 4° and an arclet length of 2.20° (90 control points). Collimator angles for fields 1, 2, 3 and 4 were 85°, 95°, 15° and 345°, respectively. Field sizes not exceeding the recommended 15 cm were selected (Ugurlu and Temelli 2020). These field sizes allow MLCs to correctly cover the PTV while blocking the hippocampi. The upper part of the PTV was covered by fields 1 and 2. Fields 3 and 4 were used to deliver radiation to the right and left hemispheres of the brain, respectively. Collimator sizes in all fields were chosen to correctly include the hippocampi. Table 3 shows the parameter settings for each of the mARC treatment fields. To make a fair comparison, the template and optimization goals were the same as in the IMRT plans. The field arrangement for the mARC plans can be seen in Fig. 2 (b).

Dosimetric evaluation

A dose-volume histogram (DVH) was generated for all PTVs and OARs for dosimetric analysis. The homogeneity index (HI) was calculated with Eq. 1 (Wu et al. 2019):

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

Where $D_{2\%}$, $D_{98\%}$ and $D_{50\%}$ represent the absorbed doses received by 2% (near maximum dose), 98% (near minimum dose), and 50% of the volume of

**Fig. 2** Field arrangement for a single patient: (a) intensity-modulated radiation therapy (IMRT) and (b) modulated arc therapy (mARC)

the PTV, respectively. An HI of 0 indicates that the absorbed-dose distribution was almost homogenous.

The conformity index (CI) was also calculated (Eq. 2) (Lin et al. 2015):

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

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. The CI value is between 0 and 1, and the closer it is to 1, the better the conformity is. 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 excluding patient positioning. MUs were also recorded for the two types of treatment for comparison.

Statistical analysis

The normality of the data was verified with the Shapiro-Wilk test. If normality could not be rejected, the t-test for paired data was applied; otherwise, the Wilcoxon signed-rank test was used. Statistical significance was set at ($p < 0.05$). The statistical analyses were performed using the OriginPro Software Version

2018 (OriginLab Corporation, Northampton, MA, USA).

Results

A senior radiation oncologist reviewed all plans for the 15 patients, assessing dose distributions and DVH properties through visual inspection, and considered all plans to be suitable for treatment (an example of dose distribution at the hippocampal level for the two techniques is shown for a single representative patient in Fig. 3). A visual comparison between both types of plans for each patient did not reveal a discernible preference for either of the two treatment techniques. The dosimetric criteria of the RTOG 0933 protocol were met in all treatment plans. The mean PTV for the 15 patients was $1,418.7 \pm 196.29 \text{ cm}^3$ (range 1,167–1,834 cm^3). Table 4 shows measurements of plan quality (HI, CI, $D_{100\%}$, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$, $D_{2\%}$, $D_{1\%}$, D_{mean} and D_{max} for the PTV) and their standard deviations (SD). The p -values with statistical significance between the two planning techniques are in bold format.

Regarding the PTV, there were significant differences for the majority of dose values delivered at a certain percentage of

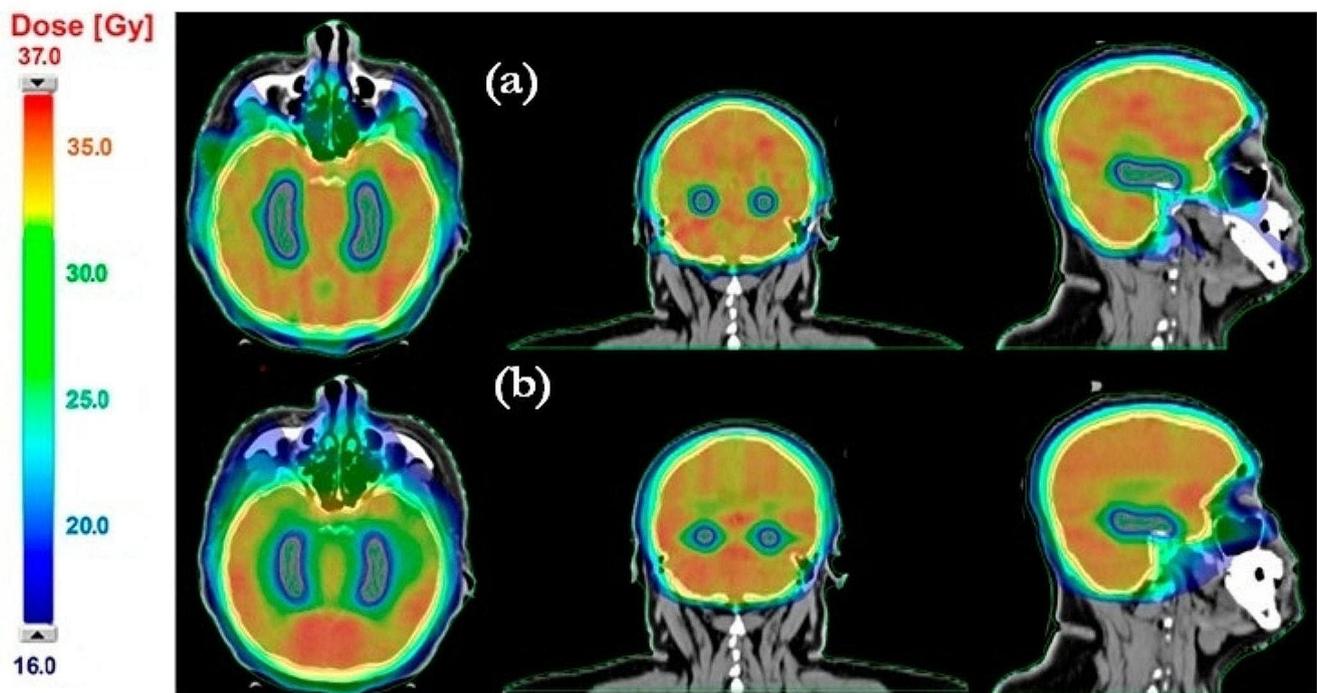


Fig. 3 Dose distribution on axial, coronal, and sagittal views for one patient: (a) intensity-modulated radiation therapy (IMRT) and (b) modulated arc therapy (mARC). The hippocampi are shown in green

Table 4 Planning target volume (PTV) Dosimetric parameters for intensity-modulated radiation therapy (IMRT) and modulated arc therapy (mARC) plans; SD – standard deviation; HI – homogeneity index (Eq. 1); CI – conformity index (Eq. 2); bold *p*-values indicate statistical significance. All plans were normalized to ensure that 90% of the PTV received a dose of 30 Gy; D_{2%} - absorbed dose received by hottest 2% of planning target volume (PTV); D_{98%} - dose received by 98% of PTV; D_{100%} - dose received by 100% of hippocampus; D_{max} - maximum dose; D_{mean} - minimum dose

Item	IMRT (mean ± SD)	mARC (mean ± SD)	<i>p</i> -value
HI	0.2769 ± 0.0360	0.2862 ± 0.0331	0.35
CI	0.8866 ± 0.0162	0.8643 ± 0.0173	0.01
D _{100%} (Gy)	10.90 ± 1.27	14.69 ± 0.55	< 0.001
D _{98%} (Gy)	24.90 ± 0.93	24.93 ± 0.62	0.87
D _{95%} (Gy)	28.67 ± 0.33	28.17 ± 0.33	< 0.001
D _{50%} (Gy)	31.85 ± 0.20	32.27 ± 0.42	< 0.001
D _{2%} (Gy)	33.72 ± 0.34	34.03 ± 0.53	< 0.01
D _{1%} (Gy)	33.98 ± 0.37	34.26 ± 0.54	< 0.01
D _{mean} (Gy)	31.49 ± 0.16	31.81 ± 0.34	< 0.001
D _{max} (Gy)	35.68 ± 0.72	35.60 ± 0.85	0.67

Table 5 Organs at risk (OARs) dosimetric parameters for intensity-modulated radiation therapy (IMRT) and modulated arc therapy (mARC) plans; SD – standard deviation; bold *p*-values indicate statistical significance between the planning techniques; D_{100%} - dose received by 100% of hippocampus; D_{max} - maximum dose; D_{mean} - minimum dose

Organ	Parameter	IMRT (mean ± SD)	mARC (mean ± SD)	<i>p</i> -value
Chiasm	D _{max} (Gy)	32.97 ± 0.93	32.97 ± 1.12	0.99
Cochlea Left	D _{mean} (Gy)	26.65 ± 2.17	29.01 ± 2.08	< 0.001
Cochlea Right	D _{mean} (Gy)	28.06 ± 2.62	28.60 ± 2.08	0.28
Eye Left	D _{max} (Gy)	18.41 ± 1.46	20.87 ± 1.56	< 0.001
Eye Right	D _{max} (Gy)	19.51 ± 2.32	20.92 ± 1.67	0.03
Hippocampus Left	D _{100%} (Gy)	8.87 ± 0.57	9.33 ± 0.83	< 0.001
Hippocampus Left	D _{max} (Gy)	14.65 ± 1.13	16.42 ± 0.98	< 0.001
Hippocampus Right	D _{100%} (Gy)	7.95 ± 0.35	9.70 ± 0.76	< 0.001
Hippocampus Right	D _{max} (Gy)	14.22 ± 1.24	16.178 ± 0.93	< 0.001
Lens Left	D _{max} (Gy)	7.44 ± 0.41	9.38 ± 0.57	< 0.001
Lens Right	D _{max} (Gy)	7.14 ± 0.71	9.85 ± 0.43	< 0.001
Optic Nerve Left	D _{max} (Gy)	30.38 ± 2.13	31.31 ± 1.43	0.06
Optic Nerve Right	D _{max} (Gy)	30.86 ± 1.93	31.92 ± 1.54	0.02

volume. The IMRT technique exhibited the highest values for D_{95%} (*p* < 0.001). The mARC delivered the highest dose values for the rest of parameters, although there were only differences with statistical significance for D_{100%}, D_{50%}, D_{2%} and D_{1%} (*p* < 0.001, *p* < 0.001, *p* < 0.01 and *p* < 0.01, respectively). For D_{98%}, mARC also showed the highest dose value but with no significant difference (*p* = 0.87). All plans exhibited high conformity and a homogeneous coverage of the PTV. The mean HI values were 0.2769 ± 0.0360 (range: 0.2480 to 0.3435) and 0.2862 ± 0.0331 (range: 0.2511 to

0.3222) for IMRT and mARC, respectively. The mean CI values were 0.8866 ± 0.0162 (range: 0.8708 to 0.9399) and 0.8643 ± 0.0173 (range: 0.8175 to 0.8838) for IMRT and mARC, respectively. Statistically significant differences were found between IMRT and mARC for CI (*p* = 0.01) but not for HI (*p* = 0.35). The homogeneity and conformity indices indicate that IMRT had better results than mARC. However, upon observing their absolute values, it can be noted that the differences are minimal, thus lacking clinical significance.

Table 5 shows the dosimetric comparison for the hippocampi and the rest of the OARs. The *p*-values with statistical significance are again in bold format. In terms of hippocampal protection, IMRT had a significantly lower D_{100%} (left hippocampus: 8.87 Gy; right hippocampus: 7.95 Gy; *p* < 0.001) for both hippocampi compared to mARC (left hippocampus: 9.33 Gy; right hippocampus: 9.70 Gy). Similarly, D_{max} for both hippocampi were lower for IMRT (left hippocampus: 14.65 Gy; right hippocampus: 14.22 Gy; *p* < 0.001) compared to mARC (left hippocampus: 16.42 Gy; right hippocampus: 16.18 Gy). The average maximum dose to the optic chiasm in IMRT and mARC was 32.97 Gy and 32.97 Gy, respectively. There were no significant differences for the D_{max} delivered to the chiasm (*p* > 0.05). In both optic nerves, IMRT showed the lowest D_{max} values. However, a statistically significant difference was only observed for the right optic nerve (*p* = 0.02). For lenses, eyes and cochleae, OARs not specifically mentioned in the RTOG 0933 protocol, the IMRT plans obtained lower D_{max} and D_{mean} values compared to mARC. More specifically, IMRT obtained lower D_{max} values for both lenses (*p* < 0.001), for left eye (*p* < 0.001) and right eye (*p* = 0.03). For both cochleae, IMRT demonstrated a lower D_{mean} compared to mARC, with a significant difference observed only for the left cochlea (*p* < 0.001). Although doses for OARs were generally higher in mARC compared to IMRT, they remained within the recommended dose limits in both cases. Therefore, the differences between both types of plans would not have influenced a clinical preference for either alternative. The average Dose-Volume Histograms (DVHs) of PTV and OARs are shown in Fig. 4.

The MUs and treatment time of the two planning techniques are shown in Table 6. The *p*-values with statistical significance are in bold format. The average total MUs in IMRT and mARC were 2419.32 ± 187.62 and 834.37 ± 85.34, respectively, representing a decrease of 65.51% (*p* < 0.001). This reduction led to a significant decrease in treatment time in mARC compared to IMRT: Mean treatment time was 852.98 ± 49.34 s and 337.33 ± 24.41 s for IMRT and mARC, respectively. This represents a reduction of 60.45% (*p* < 0.001).

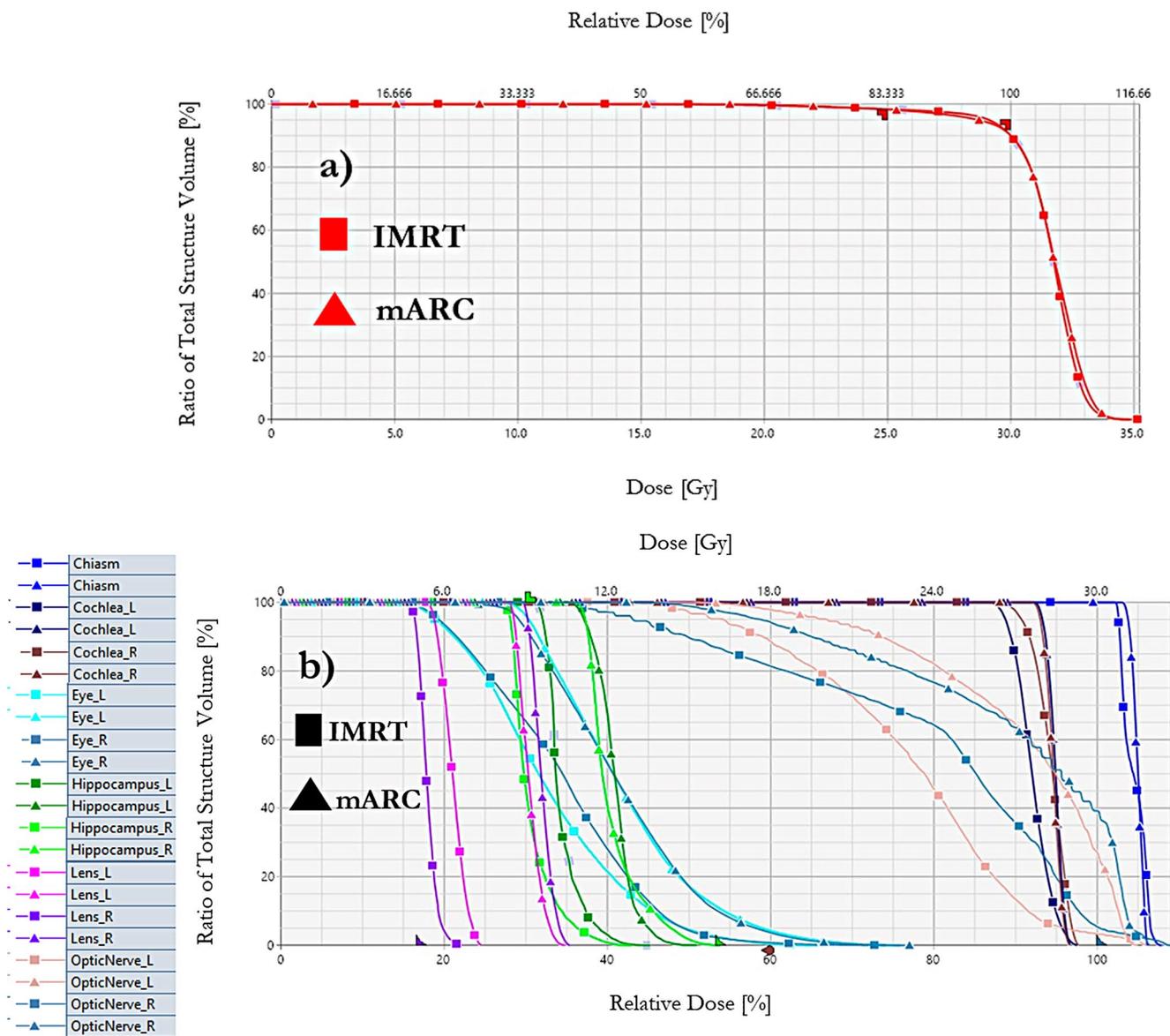


Fig. 4 Representative Dose-Volume Histograms of target volumes (a) and organs at risk (OARs) (b). All plans were normalized to ensure that 90% of the PTV volume received a dose of 30 Gy; IMRT – intensity-modulated radiation therapy; mARC – modulated arc therapy

Table 6 Monitor unit (MU) values and delivery time of treatment for IMRT and mARC; SD – standard deviation; bold *p*-values indicate statistical significance between the two planning techniques

Parameters	IMRT (mean ± SD)	mARC (mean ± SD)	<i>p</i> -value
MUs	2419.32 ± 187.62	834.37 ± 85.34	< 0.001
Time (s)	852.98 ± 49.34	337.33 ± 24.41	< 0.001

Discussion

This study demonstrates the feasibility of performing HS-WBRT by using mARC while also meeting the RTOG 0933 dosimetric criteria. Recent evidence suggests that whole brain irradiation is associated with a decline of cognitive function (Mizumatsu et al. 2003; Chang et al. 2009).

Hippocampal dose avoidance is a way to reduce neurocognitive toxicity (Gondi et al. 2010a, 2014). Advances in modern planning techniques have enabled an accurate implementation of the HS-WBRT while allowing adequate coverage of the PTV, and there are several dosimetric studies where the results obtained between IMRT, VMAT and other techniques were compared (Lee et al. 2015; Wang et al. 2015; Li et al. 2016; Gondhowiardjo et al. 2019). The present study represents the first application of HS-WBRT using the mARC technique, to the best of the authors’ knowledge. This may be relevant for radiotherapy departments equipped with a Siemens linear accelerator. The authors also consider that this study could make a valuable contribution to the literature, given that mARC represents the least widespread

arc therapy technique. Furthermore, in the present study HS-WBRT using mARC has been compared with the static IMRT technique. Specifically, results concerning plan quality (dose homogeneity and conformity) as well as dose to OARs were obtained. All plans adhered to the RTOG 0933 criteria, and even obtained satisfactory results for OARs not explicitly addressed in this protocol. All plans were normalized to ensure that 100% of the prescription dose covered 90% of the PTV. The RTOG 0933 protocol reports that such coverage is acceptable to achieve approximately 91.4% of the relative benefits of WBRT in terms of radiographically evident intracranial lesions, and it is also suggested that it would improve the time interval to neurocognitive function decline (Mehta et al. 2011). Overall, IMRT plans presented superior results compared to those of mARC. Nevertheless, the absolute differences observed in all cases were minimal, lacking any clinical relevance. These results are similar to those obtained by Gondhowiardjo et al. (Gondhowiardjo et al. 2019) where IMRT and VMAT plans for HS-WBRT were dosimetrically compared.

It is important to note that in addition to the dosimetric results, mARC plans demonstrated a substantial reduction in treatment time, with a reduction of 60.45%. This result suggests that mARC is an effective way to deliver HS-WBRT since it produces clinically acceptable plans while significantly reducing treatment time. Moreover, mARC produced plans with a much lower number of MUs (almost three times less) in comparison to IMRT plans. These results are similar to those described in previous studies. To cite a few examples, in the study by Dzierma et al. (Dzierma et al. 2014b) mARC versus IMRT plans were compared and a decrease in MUs was reported in prostate, head and neck, and hypopharyngeal patients of 22%, 20%, and 54%, respectively. For patients with hypopharyngeal carcinoma, previous studies (Bell et al. 2016b) proposed that using mARC in conjunction with flattening filter free (FFF) beam energies could save 4 to 3 min in treatment time compared to IMRT, while plan quality remained comparable or better. The reductions in the number of MUs and treatment time are of great clinical importance, since a greater number of MUs is associated with an increase in leaked and scattered radiation outside the collimator (Hall and Wu 2003). The resulting increase in radiation dose is associated with a significant increase in the possibility of developing secondary cancers (Seppala et al. 2009). This is particularly important in pediatric patients, since the incidence of radiation-induced secondary cancers is much higher for them than for adults (Hall 2006). Additionally, by requiring less MUs, the time of radiotherapy administration is considerably reduced. This is beneficial for both the patient and the medical team, since the sessions are shorter and the use of

clinical resources is optimized. In addition, the reduction in MUs implies that the patient is exposed to less radiation during treatment (Petti et al. 2006). This is especially relevant in the case of pediatric patients or those with tumours near critical organs, where minimizing the dose to healthy tissue is essential. Lastly, less MUs translates into less toxicity to surrounding tissues (Pöll et al. 2008). Side effects, such as skin irritation or fatigue, may be less pronounced compared to longer treatments (Barazzuol et al. 2020). Shorter sessions and fewer MUs make the process more comfortable for the patient. This can improve treatment adherence and quality of life during the recovery process (Fowler et al. 2004). All of the above directly benefits the patient by reducing radiation exposure and improves the overall treatment experience. This could be explained by the following reasons: the radiation fields in mARC are in a continuous state of high-speed rotational motion, a smaller MLC movement, a larger number of degrees of freedom and a smaller segment number (Dzierma et al. 2013, 2016). Another possible explanation for the above is that, in contrast to IMRT, the scattered dose for mARC is assumed to be caused by the fact that the Y jaws are fully open for IMRT in the Eclipse TPS. On the contrary, for mARC the TPS adapts the jaw and the maximum opening of the treatment field for mARC, which leads to less radiation leakage (Bell et al. 2016b).

Important differences in the administration of both types of treatment plans could lead to significantly different MUs and delivery time. The IMRT technique is associated with the delivery of a high number of MUs, and consequently longer treatment time (Lesnock et al. 2013). This is potentially detrimental to the patient, since a prolonged treatment time results in discomfort and consequently increases the possibility of patient motion, which affects the accurate delivery of the radiation dose. In particular, IMRT plans that are typically used for HS-WBRT are complicated and difficult to implement because their design is non-coplanar and requires a larger number of fields compared to mARC or VMAT (Rong et al. 2015; Wang et al. 2015; Li et al. 2016). One reason that could explain the above is the complexity of the treatment volume, since the anatomical location of the hippocampi makes dose optimization difficult, because they are completely surrounded by the PTV (Rong et al. 2015). The present study confirms what was reported in previous studies, that is, even for complex targets, the mARC technique results in shorter treatment times than those corresponding to IMRT. In the present study, the average time to deliver treatment in mARC was 337.33 s (5.62 min), which is in good agreement with other mARC studies, such as the study by Bell et al. (Bell et al. 2016a) focusing on the hypopharynx. Accuracy of treatment delivery could benefit from having only one couch position in mARC. This results in

greater comfort for the patient and fewer potential errors in couch positioning. It should be noted that treatment time values do not account for the additional time required for the radiation therapist to perform the seven couch kicks that are recommended by the RTOG 0933 protocol (Gondi et al. 2010b). Such additional couch movements inevitably contribute to further increases in treatment time.

Numerous studies have been published on the mARC technique and its dosimetric results. These studies demonstrate the mARC technique’s ability to deliver efficient and highly accurate treatments across diverse anatomical regions (Salter et al. 2011; Sarkar et al. 2015). Kainz et al. (Kainz et al. 2011) compared (in dosimetric terms, MUs and treatment time) plans in mARC with those made with tomotherapy and VMAT for head and neck, brain, prostate, and breast cancer patients. Their research revealed that mARC is capable of delivering clinically acceptable plans with dosimetric results comparable to those obtained with the other two previously mentioned techniques. However, literature also indicates that the treatment time for mARC plans is generally longer than that for plans created in VMAT. This difference is attributed to the burst delivery mode, which

interrupts the beam for MLC movement. Despite the above, mARC offers greater freedom for the configuration of MLC. And as an additional advantage in the event of an unwanted interruption of treatment, mARC allows one to accurately know the dose at any given time (Dzierma et al. 2014b).

In Table 7, MUs and treatment times from various studies are compared with those obtained in the present study (Wang et al. 2015; Li et al. 2016; Yuen et al. 2020; Sprowls et al. 2021). In all those studies, the criteria for dose prescription, contouring, and plan evaluation of the RTOG 0933 protocol were followed. It is noteworthy that the number of MUs for the present study is comparable to those reported in other VMAT studies, and significantly lower than those reported by studies focusing on IMRT. The authors consider that this establishes the mARC technique as a viable option with its own advantages for its implementation in HS-WBRT.

There are several research topics where the development of a mARC plan can be further investigated. For example, there is no consensus on which technical parameters would produce the best dosimetric performance along with a shorter treatment time. Nor has a systematic evaluation of performance in mARC been made in terms of MUs and treatment time. In studies such as those by Dzierma et al. (Dzierma et al. 2016), it is suggested that parameters such as the number and length of the arclets and distance of movement of the MLC generally influence treatment time. An arclet length of 2.20° spaced every 4° was used in the present study. Previous studies have indicated that the treatment time increases as smaller arclets are used (minimum arclet length 2° separated every 4°) (Dzierma et al. 2016). Hence, it is expected that the results of the present study would closely align with optimal treatment efficiency for mARC.

It has even been proposed that the treatment time in mARC could be strongly affected by the TPS used (Dzierma et al. 2015). Furthermore, it is argued that complex PTVs (such as those used for HS-WBRT) require more arclets and MUs to obtain a plan with good quality (Dzierma et al. 2016). These parameters have not yet been fully explored for HS-WBRT treatments in mARC. Additionally, the effect of reducing the time that would be obtained by using FFF energy beams during a HS-WBRT has not been explored either. Bell et al. (Bell et al. 2016a) reported that using 7 MV FFF beams together with mARC would reduce treatment time by a factor of 2 compared to 6 MV IMRT. This is interesting because the absence of a flattening filter leads to a reduction in the scattered dose per MU (Kragl et al. 2011; Dzierma et al. 2014a). However, FFF energy beams were not used in the present study, suggesting that treatment time could be even further reduced.

Table 7 Number of Monitor Units (MUs) and treatment time of the present study and those reported in previously published studies for hippocampal sparing whole brain radiotherapy (HS-WBRT); SD – standard deviation; IMRT – intensity-modulated radiation therapy; mARC – modulated arc therapy; VMAT – volumetric modulated arc therapy

	mean ± SD				
	Num-ber of patients	Beam description	Num-ber of beams	MU	Treat-ment time (s)
Present study (mARC)	15	Coplanar partial arcs	4	834.37 ± 85.34	337.33
Wang et al. 2015 (IMRT)	10	Non coplanar	7	2,883 range: 2,706–3,258	576.6
Wang et al. 2015 (VMAT)	10	Coplanar arcs 358° length (each)	2	887 range: 701–983	150
Li et al. 2016 (IMRT)	10	Non coplanar	7	2,863 range: 2,338–3,319	573
Li et al. 2016 (VMAT)	10	Coplanar arcs 358° length (each)	2	935 range: 840–1,120	150
Yuen et al. 2020 (VMAT)	20	Coplanar Partial arcs	4	1,085.58 ± 153.57	217.2
Sprowls et al. 2021 (VMAT)	10	Coplanar arcs 358° length (each)	2	800.7 ± 37.8	162

Conclusions

The purpose of this study was to evaluate the mARC technique as a planning and treatment solution for HS-WBRT following the dosimetric criteria of RTOG 0933. Here, these criteria were included and the dosimetric results of mARC were compared with those of IMRT (9 non-coplanar fields). Relevant metrics such as the number of MUs and treatment time were also reported. The results demonstrate the feasibility of using the mARC technique as a treatment option for HS-WBRT. The main advantage of mARC over IMRT is a significant decrease in MUs and treatment time while meeting the RTOG dosimetric criteria. The reduction in MUs translates into a reduction in the additional dose of scattered radiation which in turn reduces the risk of developing secondary cancers. It is concluded that the mARC technique can be considered a practical and viable option for HS-WBRT, particularly in workplaces where it is necessary to limit the treatment time per patient as much as possible.

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Author contributions E.A. Martín-Tovar conceived the original idea, wrote the manuscript, created half of treatment plans, and developed the statistical analyses. A.H. Badillo-Alvarado and J.L. Gaxiola-Sosa performed the patient contouring, designed the study inclusion criteria, and performed all clinical evaluations. L.E. Cocom-Poot created the other half of treatment plans and prepared all the Figures. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Declarations

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

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare that they have no conflict of interest.

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 Transparencia, Acceso a la Información y Protección de Datos Personales) on Research for Health and Protection of Personal Data, respectively.

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