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A New Approach to Highly Conformal Hippocampal-sparing Whole-brain Radiotherapy: A Feasibility Study

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Abstract

Background/Aim: Hippocampal-sparing whole-brain radiotherapy (HS-WBRT) is increasingly used for multiple brain metastases. However, most studies have not reported dose conformity indices (*CI*). In the only study indicating the *CI*, conformity was low (*CI*=0.7). We developed a new technique to achieve a significantly higher *CI* and better dose coverage.

Patients and Methods: Ten patients received 30 Gy of HS-WBRT for brain metastases. Three variants of treatment plans (VAR1, VAR2, VAR3) were investigated. Volumetric modulated arc therapy plans with two (2ROT) or three rotations (3ROT) were created for each variant. Plans were compared for compliance with hippocampal sparing criteria, *CI* (where a higher value indicates better conformity), and homogeneity index (*HI*, where a lower value indicates better homogeneity).

Results: Best results (highest *CI*, lowest *HI*) were achieved with the VAR3-3ROT technique (a new method), which yielded a *CI*=0.92-0.95 and a *HI*=0.05-0.09. VAR3-2ROT led to a *CI*=0.90-0.95 and a *HI*=0.06-0.11. With the other techniques, *CI* and *HI* ranged between 0.77-0.87 and 0.15-0.32, respectively.

Conclusion: Our new technique achieved both appropriate hippocampal sparing and very high dose conformity of ≥0.9. Significant underdosage outside the hippocampal-sparing area was avoided.

Keywords: Hippocampal sparing, whole-brain radiotherapy, dose conformity, neurocognition, brain metastases.

Introduction

Since medical advancements continue to improve the overall prognosis of cancer patients, the incidence of brain metastases is increasing (1). Being the most common intracranial malignancy in adults, up to 20% of patients are confronted with brain metastases during the onset of their disease (2-6). Most common primaries associated with brain metastases include cancers of the lung, kidney, breast, colon, and skin (malignant melanoma) (3-6). Besides

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surgery, local therapeutic approaches include stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT). In 2022, the American Society for Radiation Oncology (ASTRO) released a clinical practice guideline on radiation therapy for brain metastases (7). The ASTRO task force recommends SRS for patients showing a good Eastern Cooperative Oncology Group performance status (ECOG-PS of 0-2) and up to four intracranial lesions (conditionally recommended in case of up to 10 brain metastases) (7, 8). In contrast, WBRT is reserved for patients with a higher intracranial tumor burden. A very commonly used fractionation regimen of WBRT applies a total dose of 30 Gy given in ten fractions. Neurocognitive deterioration is one of the most feared consequences of WBRT (7). Patho-physiologically, neuroinflammation, demyelination, and vascular damage appear to be the causes of cognitive decline (9, 10). Besides prescribing potentially neuroprotective medication (*e.g.,* memantine) (11), radiotherapeutic approaches include hippocampal-sparing WBRT (HS-WBRT) (7, 12). Being crucial for memory function, a dose reduction to the hippocampal area in HS-WBRT helps in preserving the patients' cognitive status compared to standard WBRT (13). Since the risk of (peri-)hippocampal relapse of brain metastasis is low (10, 14-16), HS-WBRT is considered a safe method.

Since the 2000s, various approaches of HS-WBRT have been proposed demonstrating their feasibility by means of linear accelerator (LINAC)-based intensity-modulated radiation therapy (IMRT), tomotherapy or volumetric modulated arc therapy (VMAT) (17, 18). However, no clear specifications on the underlying medical-physical planning procedure have been made by most authors (13, 15, 19). Moreover, most studies did not report dose conformity indices (*CI*). In the only study indicating the *CI*, conformity was low (*CI*=0.7). A low *CI* indicates underdosage of HS-WBRT in areas of the brain outside the hippocampal-sparing region, which may be associated with a higher risk of an intracerebral recurrence of the metastatic disease. Thus, a novel and reproducible technique is desirable that achieves both appropriate hippocampal sparing and a higher *CI* than 0.7. Therefore, the present study was performed. To our knowledge, this is the first analysis investigating and comparing different approaches for dose conformity and homogeneity in HS-WBRT. Based on this, we have developed a refined and improved technical approach, which allows hippocampal sparing in a highly conformal manner.

Patients and Methods

Ten patients (six males, four females, age 55-81 years) treated with HS-WBRT were included in this retrospective study. All patients underwent a non-contrast enhanced planning CT (computed tomography) acquisition with 3 mm slice thickness. CT imaging was performed using a 40-slice CT scanner type Biograph mCT (Siemens AG, Erlangen, Germany). For imaging processing and target volume delineation, planning CTs were transferred to the ARIA® oncology information system (Version 16.0, Varian Medical Systems, Palo Alto, CA, USA). Dose calculations were performed by the treatment planning system (TPS) Eclipse™ (Version 16.1, Varian Medical Systems).

Target volume delineation. The patients received 3-dimensional gadolinium-enhanced magnetic resonance imaging (MRI) of the head prior to HS-WBRT. The axial contrast-enhanced T1 sequence and the FLAIR sequence were fused semi-automatically with the acquired planning CT. Bilateral contouring of the hippocampal area was based on the contrast-enhanced T1 sequence as previously described (18). Delineation of the hippocampal-sparing area involved the volumetric expansion of the hippocampal contour by 7 mm to address the necessary dose reduction between the hippocampus and the entirety of the planning target volume (PTV) encompassing the whole brain.

Treatment planning. Two types of VMAT plans were created to be treated at a CLINAC 2100 DHX (Varian Medical Systems), equipped with a Millenium 120 Multi leaf collimator (MLC). The first type of treatment plan consisted of two counter-rotating 360° arc fields (2ROT)

with collimator settings at 30˚ and 330˚. Field sizes were specified by the treatment planning software (TPS). The second type of treatment plan (3ROT) was extended by an additional third rotation field at a collimator setting of 90˚. This collimator position enabled vertical MLC movement between the hippocampi. Thus, filling of the interstitial space was performed more efficiently when compared to two rotational fields.

The field size of the y-aperture (perpendicular to the leaves) was set to 6 cm, ensuring that the hippocampi were completely included into the beams eye views. The x-aperture was adjusted to the anatomy of the brain. For dose calculation, the ACUROS XB dose calculation algorithm (Version 16.1.2, Varian Medical Systems) was applied. All plans were calculated with a photon energy of a 6MV spectrum with a dose rate of 600 MU/min. The isocenter (IC) was set in the middle of the brain, above the hippocampi.

Table I. *Dose acceptance criteria for Planning Target Volume (PTV). Dx% represents the minimum dose to x% of the structure's volume. Hippocampal dose acceptance criteria include Dmean and Dx%.*

	PTV dose constraints		
D_{PTV} (x%)	Variant 1+2 (18, 21)		Variant 3
	Optimal	Mandatory	
D_{98}	23.5	22.5	28.5
D_{95}	26	25	29
D_{90}	27.5	26.5	29.2
D_{50}	30	30	30
	Hippocampus dose constraints		
D_{Hippo} (x%)	Variant 1 (VAR1) (21)	Variant 2 (VAR2) (14, 18, 20)	Variant 3 (VAR3)
D_{mean}	≤10 Gy	Not in use	≤14.0 Gy
D_{98}	Not in use	≤9 Gy	≤10 Gy
D_2	Not in use	≤17 Gy	≤19 Gy

Dose constraints and acceptance criteria. Dose acceptance criteria for the PTV and the hippocampal area are summarized in Table I. Three planning variants with different target constraints were defined (VAR1-3). The constraints for VAR1 and VAR2 are based on previously published literature (13, 15, 18-21), whereas the constraints of VAR3 were routinely used in our department. For each planning CT, separate treatment plans were calculated for VAR 1, VAR 292, and VAR3 using 2 ROT and 3 ROT. This resulted in six plans for each CT and 60 plans in total. All plans were compared regarding the compliance of the PTV with hippocampal-sparing dose criteria, *CI* and homogeneity index (*HI*).

The *CI* is calculated as $CI = \frac{TV_{RI} \times TV_{RI}}{TV \times V_{RI}}$ (equation 1).

where *TV* stands for target volume, for the volume of the reference isodose, and for the target volume, which is covered by the reference isodose (22).

The *HI* is defined as $HI = \frac{D_{PTV}(2\%) - D_{PTV}(98\%)}{D_{PTV}(50\%)}$

(equation 2),

where refers to the dose receiving x% of the PTV volume.

The *CI* calculated according to Equation 1 refers to the volume of whole brain PTV that is large compared to the volume of the hippocampi. A reduced dose coverage in the area of the hippocampi would possibly not or only barely be noticeable in the *CI*. Therefore, a quality measure CI_{HipReg} was defined, which is limited to a 3 cm extension around the hippocampi. For this purpose, equation 1 was modified into equation 3 as follows:

$$CI_{HipReg} = \frac{VOI2_{RI} \times VOI2_{RI}}{VOI2 \times V_{RI\_HippEx}}$$ (equation 3).

An extended hippocampus volume (V_{HippEx}) was defined, created by applying a 3 cm 3D-margin around the hippocampi, located inside the PTV-WB. The $V_{RI\_VHippEx}$ in equation 3 contains the volume of the 95% isodose that is only located within V_{HippEx} and replaces V_{RI} in equation 1. The TV in equation 1 was replaced by a volume of interest (VOI), which corresponds to the PTV WB-Hippo within V_{HippEx}.

VOI_{RI} is the volume of the VOI, which is covered by the RI and corresponds to TV_{RI} in equation 1. Thus, with

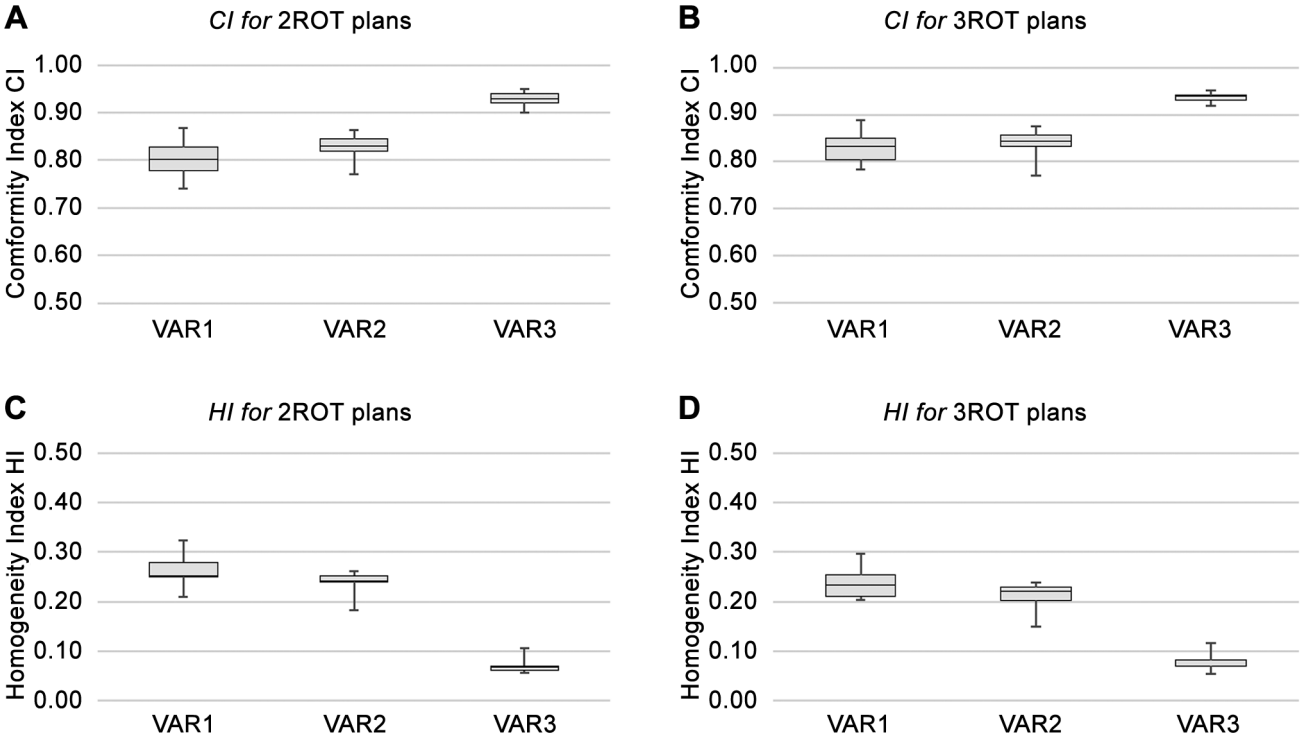

Figure 1. *Dose conformity (CI) and homogeneity (HI) indices of all plan variants.*

equation 3, a modified $CI_{HippReg}$ can be calculated, which only considers an area of 3 cm around the hippocampi. However, The $CI_{HippReg}$ does not correspond to a *CI* according to van't Riet *et al.* (22), as it does not include any RI outside V_{HippEx}. $CI_{HippReg}$ is merely an auxiliary variable to determine whether the conformation at the hippocampi becomes smaller or larger.

Results

Dose CI and HI. Best results (highest *CI*, lowest *HI*) were achieved with VAR3-3ROT (our new technique) with *CI* values ranging between 0.92 and 0.95 and *HI* values ranging between 0.05 and 0.09. VAR3-2ROT was associated with *CI* values of 0.90-0.95 and *HI* values of 0.15-0.25. With VAR1-2ROT, the *CI* ranged between 0.74-0.87, with 0.74 being the lowest *CI* value observed overall. The corresponding *HI* range was between 0.21 and 0.32, where 0.32 was the highest *HI* value observed in our study. For VAR1-3ROT, the values were *CI*=0.78-0.88 and *HI*=0.2-0.28.

VAR2-2ROT attained values for *CI* in the range of 0.77-0.86 and for *HI* in the range of 0.18-0.26. For VAR3-3ROT, the *CI* range was 0.77-0.88, and the *HI* range was 0.15-0.25. All results are visualized in Figure 1 as a box plot, providing an overview of the data distribution.

Dose conformity $CI_{HippReg}$ at the hippocampal area. For VAR1-2ROT, the $CI_{HippReg}$ was in the range of 0.28-0.72. For VAR1-3ROT the range was 0.52-0.88. The achieved values for VAR2-2ROT were 0.31-73 and for VAR2-3ROT 0.52-84. VAR3-2ROT obtained a $CI_{HippReg}$ range of 0.79-0.96. The highest dose conformity at the hippocampal area was achieved with VAR3-3ROT with $CI_{HippReg}$=0.91-0.99. The dose conformity indices $CI_{HippReg}$ at the hippocampal area within the structure VOI are listed in Table II. In addition, Figure 2 illustrates dose distributions in a representative transversal plane of all three planning variants. Figure 2A

shows the dose distribution of a plan calculated according to VAR1-3ROT. The 95% isodose is located at approximately 2 cm from the hippocampi, and *CI* was *0.82*. The irradiation plan, which was calculated according to VAR2-3ROT (Figure 2B), reduced the distance to approximately 0.8 cm. The corresponding *CI* was *0.85*. In a plan according to VAR3-3ROT (Figure 2C), the 95% isodose was located at approximately 0.2 cm from the hippocampi (*CI=0.94*).

Dose-volume histogram. Figure 3 demonstrates a comparison DVH of irradiation plans Type VAR1_ROT2 and VAR1_ROT3. With 3ROT, the PTV coverage (red lines) and hippocampal protection were superior compared to 2ROT (blue lines). As shown from the green curves, the dose coverage within the VOI, *i.e.*, the close hippocampal area, improved by adding the third rotation. This behavior is typical and can be observed between all 2ROT and 3ROT plans.

Discussion

High dose conformity in treatment planning of radiotherapy is important in order to achieve optimal treatment outcomes (23). In the present study, we refined the technical approach for optimizing dose conformality and homogeneity in the hippocampal area by means of a third rotation field in patients irradiated for brain metastases. Obviously, hippocampal sparing should be considered in the context of various fractionation concepts. Overall, most working groups applied a cumulative dose of 30 Gy over a varying number of radiotherapy sessions (15, 18-20). In accordance, our patients received HS-WBRT of 30 Gy in 10 fractions with a 7 mm volumetric expansion around the hippocampus. While Grosu *et al.* and Popp *et al.* choose the same volumetric expansion of 7 mm, other authors defined a narrower volumetric margin of 5 mm (12, 15, 19, 20). Dose constraints, which have been considered safe for neurocranial irradiation are summarized in Table III. The doses we used were chosen in accordance with previously published data.

Table II. *Conformity, represented as $CI_{HippReg}$ for all CT data sets, calculated for both treatment types - two arc rotations (2ROT) and three arc rotations (3ROT) - across doses acceptance variants 1-3.*

	$CI_{HippReg}$ Variant 1		$CI_{HippReg}$ Variant 2		$CI_{HippReg}$ Variant 3	
CT #	2 ROT	3 ROT	2 ROT	3 ROT	2 ROT	3 ROT
1	0.49	0.59	0.71	0.82	0.89	0.92
2	0.71	0.77	0.64	0.77	0.94	0.96
3	0.45	0.53	0.42	0.52	0.79	0.92
4	0.70	0.85	0.73	0.84	0.96	0.97
5	0.28	0.52	0.31	0.57	0.80	0.91
6	0.72	0.88	0.63	0.71	0.97	0.99
7	0.56	0.68	0.56	0.71	0.96	0.97
8	0.63	0.77	0.69	0.79	0.95	0.96
9	0.63	0.76	0.65	0.79	0.94	0.95
10	0.57	0.72	0.63	0.73	0.95	0.96

For our chosen prescription dose of 30 Gy (3 Gy per fraction), we achieved mean and maximum hippocampal doses of <14 Gy and <26 Gy, respectively. In comparison, Gondi *et al.* performed a comparative study on hippocampal sparing contrasting helical tomotherapy and IMRT, applying 30 Gy in 10 fractions (18). These authors stated that tomotherapy was superior considering hippocampal sparing compared to LINAC-based IMRT (5.5 Gy median and 12.8 Gy maximum doses for tomotherapy, 7.8 Gy median and 15.3 Gy maximum dose for IMRT). In our case, LINAC-based VMAT was available at our institution.

Dose constraints for HS-WBRT based on previously published studies are shown in Table III. In VAR1 and VAR2, the PTV constraints D_{98}≥23.5 Gy, D_{95}≥26 Gy, D_{90}≥27.5 Gy, and D_{50}≥30 Gy were adapted, as there is a good agreement with most of the available studies (15, 19-21). With a total dose of 30 Gy, the 25 Gy of D_{98} corresponds to only 83% of the prescription dose, whereas a D_{mean} of 35 Gy, as suggested by Grosu *et al.*, corresponds to 116% (19). The International Commission on Radiation Units (ICRU) 50 report suggests for the PTV a dose range of 95-107% (24). Therefore, stricter constraints were defined for VAR3, where 98% of the PTV should receive at least 95% of the prescribe dose, *i.e.*, ≥28.5 Gy. These definitions are not strictly adopting the

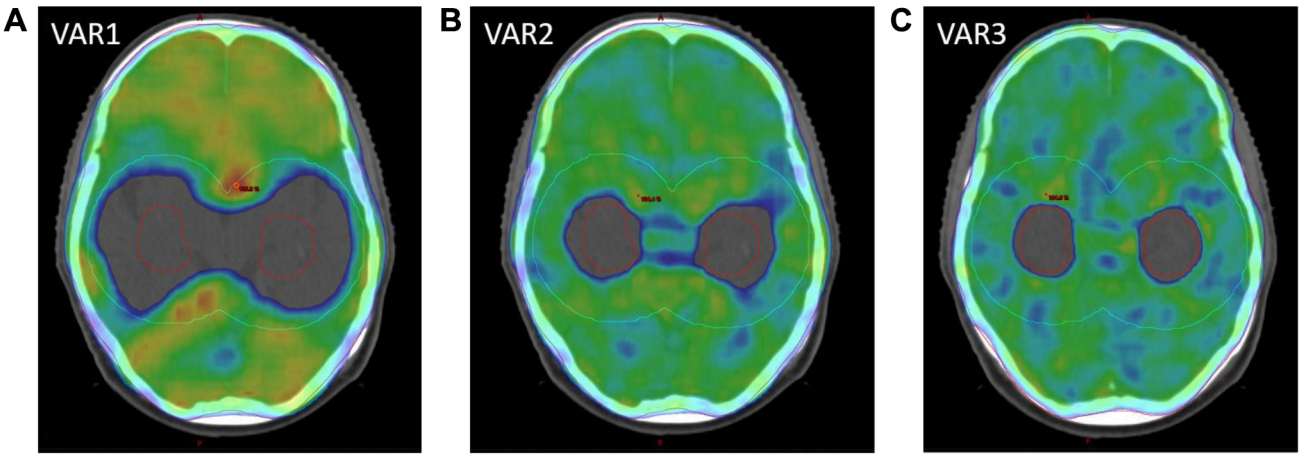

Figure 2. *Whole brain irradiation with hippocampus sparing. Dose coverage in color wash from 95% to 107%. Representative transversal plane in CT#2. Irradiation plans were calculated according to the planning type with three arc rotations (3ROT). A) Plan for variant 1 (VAR 1). B) Plan for variant 2 (VAR 2). C) Plan for variant 3 (VAR 3). The planning target volume (PTV) is shown in red, and the auxiliary structure volume of interest 1 (VOI1) in cyan.*

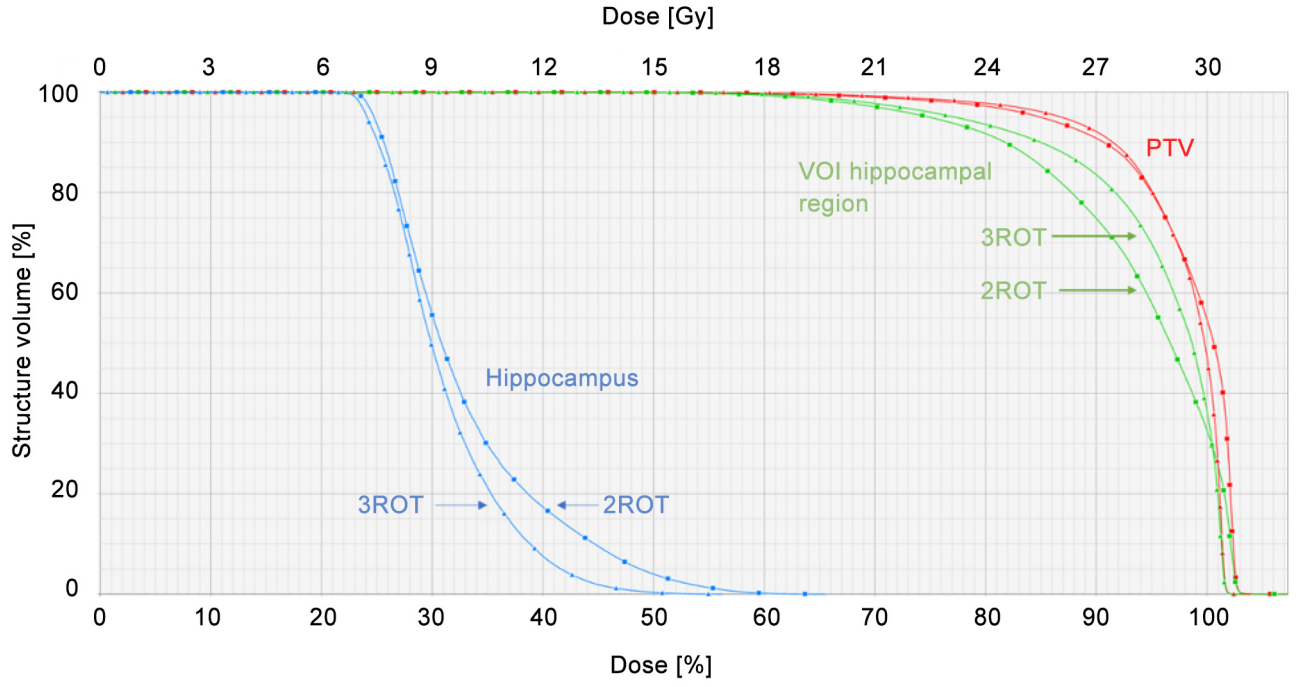

Figure 3. *Dose-volume histogram for the planning target volume (PTV) and the volume of interest 2 (VOI2) area in the hippocampal area and hippocampi, shown exemplarily for variant 1 (VAR1). Squares represent 2ROT and triangles represent 3 ROT.*

ICRU guideline mentioned above, but approximating it, knowing well that in reality these values would be difficult to achieve, especially in the cranial margin areas and in the areas close to the hippocampi. Nevertheless, the aim of these constraints is to achieve high quality conformity in the immediate surroundings of the hippocampi.

Table III. *Dose constraints for hippocampus avoidance during whole brain radiotherapy based on previously published studies.*

	N patients	RT-dose (whole brain)	Volumetric expansion around hippocampal area (mm)	Dose constraints	
				Hippocampus	Whole Brain PTV
Our study	10	10×3 Gy	7	LINAC-based VMAT D_{mean}≤14 Gy $D_{98\%}$≤10 Gy $D_{2\%}$≤19Gy	LINAC-based VMAT $D_{98\%}$≥28.5 Gy $D_{95\%}$≥29 Gy $D_{50\%}$≥30Gy
Gondi *et al.* (18)	5	10×3 Gy	5	Helical tomotherapy: D_{max}: 6 Gy 3 Gy to ≤20% LINAC-based IMRT: D_{max}: 11 Gy 9 Gy to ≤40% Helical tomotherapy/ hippocampal avoidance volume): D_{max}: 30 Gy 20 Gy to ≤20%	Helical tomotherapy: D_{max}: 30 Gy 30 Gy to ≥96% LINAC-based IMRT: D_{max}: 34 Gy D_{min}: 32 Gy No dose constraints for hippocampal avoidance volume applicable.
Grosu *et al.* (HIPPORAD-trial) (19)	132	HS-WBRT+SIB *versus* WBRT+SIB WBRT: 12×2.5 Gy SIB: 51/42 Gy	7	LINAC & Tomotherapy HS-WBRT-arm (experimental arm): $D_{98\%}$≤9 Gy $D_{2\%}$≤17 Gy WBRT-arm (control arm): $D_{98\%}$ ≥25 Gy	Both treatment arms: $D_{98\%}$≥25 Gy D_{mean}≤35 Gy
Popp *et al.* (15)	62	HS-WBRT+SIB WBRT: 12×2.5 Gy SIB: 51/42 Gy	7	Analogous to the HIPPORAD Trial Protocol $D_{98\%}$≤9 Gy $D_{2\%}$≤17 Gy D_{mean}≤10 Gy	–
Megias *et al.* (HIPPO trial) (20)	n/a[1]	10×3 Gy	5	D_{mean}<10Gy $D_{2\%}$<15 Gy	$V_{98\%}$: 23.5 Gy $V_{95\%}$: 26 Gy $V_{90\%}$: 27.5 Gy $V_{50\%}$: 30 Gy $V_{2\%}$: 33 Gy
Brown *et al.* (13)	261[2]	HS-WBRT *versus* WBRT 10×3 Gy	5	$D_{100\%}$ ≤9 Gy D_{max}≤16 Gy (dose to the hottest 0.03-cc volume of bilateral hippocampi)	$D_{2\%}$≤37.5 Gy $D_{98\%}$≥25 Gy V30Gy ≥95%

[1]No number of patients is reported. However, the data overview mentions 11 planning benchmark cases. [2]Number refers to patients allocated to HS-WBRT+memantine. HS-WBRT: Hippocampus avoidance whole brain radiotherapy; RT: radiotherapy; SIB: simultaneous integrated boost; D_{max}: maximum dose, D_{min}: minimum dose, D_{mean}: Mean dose; LINAC: linear accelerator; IMRT: intensity-modulated radiotherapy; $D_{x\%}$: Minimum dose to x% of the structure's volume; n/a: not applicable; HS-WBRT: hippocampus avoidance whole brain radiotherapy.

For VAR 1, a D_{mean}<10 Gy was defined as the only constraint for the hippocampi. This is already an ambitious target when a total dose of 30 Gy is administered. In contrast to Popp *et al.*, for VAR2 a D_{mean} was omitted, but less strict hippocampal constraints D_{98}<9 Gy and D_2<17 Gy were defined. In VAR3, priority was given to high dose conformity of the PTV. To meet this, a less strict hippocampal constraint D_{mean}<14 Gy was defined.

The *CI* (2 ROT and 3 ROT grouped together) of VAR1 (0.74-0.88) and VAR2 (0.77-0.88) were clearly below the

CI of VAR 3 (0.92-0.95). On the one hand, this was due to the low constraints defined for the hippocampi, which force a dose drop of 67% to 70%. On the other hand, it was due to the dose constraint for the PTV, as with D_{98}≥23.5 Gy only a level of 78% of the prescribed dose had to be achieved. However, this was also necessary, as otherwise the constraints for the hippocampi could not be achieved. For VAR3, the minimum dose coverage requirement of the PTV of D_{98}≥28.5 Gy led to a high *CI* anyway, but this was not limited by a less strict Hippo D_{mean}≤14 Gy.

The *CI* of VAR1 and VAR2 were similar. However, when looking at the mean values of *CI* VAR1 2ROT (0.81) and 3ROT (0.83), as well as of *CI* VAR2 2ROT (0.83) and 3ROT (0.85), a higher conformity was achieved with VAR2 than with VAR1, even if only marginal. This led to the conclusion that a mean dose constraint of the hippocampi <10 Gy might be too strict. Compared to 2ROT, the use of 3ROT led to higher *CI* in 19 cases and to constant *CI* in 11 cases. Of these 11 cases, 5 occurred in VAR2 and 6 in VAR 3. The increase in *CI* from 2ROT to 3ROT only occurred in a *CI* range of 0.01-0.06 across all plans, which initially appeared negligible. However, it should be kept in mind that *CI* is determined over the entire WB volume, which is always quite large when compared to the volume of the hippocampi. Dose gaps that only occur in the vicinity of the hippocampi are unlikely to be noticeable in the *CI*. However, dose coverage in the area of the hippocampi is of particular interest, as the gap to the whole brain PTV should be as small as possible. Looking at the CI_{HipReg} we defined, it can be clearly observed that the CI_{HipReg} increased for all 3ROT plans compared to the 2ROT plans. The introduction of a third support rotation therefore led to an improvement in dose coverage, particularly in the hippocampal area. Figure 2 and Figure 3 support these statements. Figure 2 shows dose distributions (color wash of 95%-max%) of VAR1-3 in a representative CT as well as in a representative plane. It can be seen how the dose coverage increased in quality from VAR1 to VAR2 and to VAR3. In addition, the VOI is shown in each case and illustrates the size relationships between hippocampi, PTV and dose coverage. In the DVH shown in Figure 3, the influence of the third support rotation can be observed. The additional rotation led to a reduction in the dose in the hippocampi and, at the same time, to an increase in dose conformity in the VOI. In contrast, the dose conformity over the much larger WB volume increased only marginally.

By looking at Figure 2, the question arises as to whether the concept of PTV margins around the hippocampi is indirectly softened, *i.e.* enlarged, due to unwanted reduction of the radiation dose in the hippocampi. Figure 2, as well as the *CI* values, demonstrates that only with VAR3 a PTV dose coverage of high quality was achieved. Furthermore, the boxplots demonstrate that the third rotation tends to support a lowering of the hippocampal dose. The *CI* increases continuously from VAR1 to VAR2 to VAR3.

An additional influence on the quality of the homogeneity by a third rotation could not be determined. Megias *et al.*, Popp *et al.*, and Brown *et al.* did not provide *CI* and *HI* values in their studies (12, 15, 20). Kraft *et al.* reported values of *CI*=0.7 calculated according to van't Riet *et al.* (21, 22). Their treatment plans were calculated for Varian Halcyon® and Elekta Synergy® radiotherapy devices. All plans in the present study had *CI* >0.7 according to the method of van't Riet *et al.* and, thus, achieved a higher conformity than the plans in the study of Kraft *et al.* (21, 22).

In addition to the retrospective nature of our analysis, the fact that no clinical correlation is possible constitutes a further limitation of our analysis. Accordingly, it is not possible to verify whether and to what extent higher conformality and dose homogeneity had a positive effect on the improvement of our patients' cognitive performance. In addition to WBRT, there are other possible confounders (*e.g.*, previous illnesses, previous medication, and systemic treatment) that may have an impact on neurocognitive function. Moreover, it remains unclear whether the significant improvement of the *CI* associated with less underdosage outside the hippocampal-sparing area really reduces the rate of intracerebral recurrences. Answering this question is

particularly important, since the higher *CI* was only achieved at the cost of a higher mean dose at the hippocampi. It is also necessary to evaluate whether this difference is associated with a significantly higher risk of neuro-cognitive decline. Prospective trials are required to properly answer these questions.

In summary, despite a prescribed total dose of 30 Gy and a volumetric margin around the hippocampal area of 7 mm, we were able to reduce the mean hippocampal dose to 14 Gy and achieved an excellent conformity of >0.9 to the volume outside the hippocampal-sparing area. An additional field with 90˚ collimator rotation improved the dose coverage, particularly in the area surrounding the hippocampi. Significant underdosage outside the hippocampal-sparing area was avoided at the cost of a higher mean dose at the hippocampi. Prospective clinical trials are required to identify the differences regarding the risk of intracerebral recurrences and neuro-cognitive deficits between our new technique and other approaches.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

All Authors participated in the design of the study. Data were collected by C.Z. and A.L. C.Z. and D.R. drafted the article, which was reviewed and approved by all Authors.

References

1 Singh K, Saxena S, Khosla AA, McDermott MW, Kotecha RR, Ahluwalia MS: Update on the management of brain metastasis. Neurotherapeutics 19(6): 1772-1781, 2022. DOI: 10.1007/s13311-022-01312-w

2 Saha A, Ghosh SK, Roy C, Choudhury KB, Chakrabarty B, Sarkar R: Demographic and clinical profile of patients with brain metastases: A retrospective study. Asian J Neurosurg 8(3): 157-161, 2013. DOI: 10.4103/1793-5482.121688

3 Johnson JD, Young B: Demographics of brain metastasis. Neurosurg Clin N Am 7(3): 337-344, 1996.

4 Nayak L, Lee EQ, Wen PY: Epidemiology of brain metastases. Curr Oncol Rep 14(1): 48-54, 2012. DOI: 10.1007/s11912-011-0203-y

5 Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G: Epidemiology of metastatic brain tumors. Neurosurg Clin N Am 22(1): 1-6, 2011. DOI: 10.1016/j.nec.2010.08.007

6 Singh R, Stoltzfus KC, Chen H, Louie AV, Lehrer EJ, Horn SR, Palmer JD, Trifiletti DM, Brown PD, Zaorsky NG: Epidemiology of synchronous brain metastases. Neurooncol Adv 2(1): vdaa041, 2020. DOI: 10.1093/noajnl/vdaa041

7 Gondi V, Bauman G, Bradfield L, Burri SH, Cabrera AR, Cunningham DA, Eaton BR, Hattangadi-Gluth JA, Kim MM, Kotecha R, Kraemer L, Li J, Nagpal S, Rusthoven CG, Suh JH, Tomé WA, Wang TJC, Zimmer AS, Ziu M, Brown PD: Radiation therapy for brain metastases: an ASTRO clinical practice guideline. Pract Radiat Oncol 12(4): 265-282, 2022. DOI: 10.1016/j.prro.2022.02.003

8 Schiff D, Messersmith H, Brastianos PK, Brown PD, Burri S, Dunn IF, Gaspar LE, Gondi V, Jordan JT, Maues J, Mohile N, Redjal N, Stevens GHJ, Sulman EP, van den Bent M, Wallace HJ, Zadeh G, Vogelbaum MA: Radiation therapy for brain metastases: ASCO guideline endorsement of ASTRO guideline. J Clin Oncol 40(20): 2271-2276, 2022. DOI: 10.1200/JCO.22.00333

9 Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S: Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol 13(1): 52-64, 2017. DOI: 10.1038/nrneurol.2016.185

10 Leskinen S, Shah HA, Yaffe B, Schneider SJ, Ben-Shalom N, Boockvar JA, D'Amico RS, Wernicke AG: Hippocampal avoidance in whole brain radiotherapy and prophylactic cranial irradiation: a systematic review and meta-analysis. J Neurooncol 163(3): 515-527, 2023. DOI: 10.1007/s11060-023-04384-6

11 Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, Choucair A, Fox S, Suh JH, Roberge D, Kavadi V, Bentzen SM, Mehta MP, Watkins-Bruner D, Radiation Therapy Oncology Group (RTOG): Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 15(10): 1429-1437, 2013. DOI: 10.1093/neuonc/not114

12 Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L, Mehta MP: Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol 32(34): 3810-3816, 2014. DOI: 10.1200/JCO.2014.57.2909

13 Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS, Bovi JA, Robinson C, Konski A, Khuntia D, Grosshans D, Benzinger TLS, Bruner D, Gilbert MR, Roberge D, Kundapur

V, Devisetty K, Shah S, Usuki K, Anderson BM, Stea B, Yoon H, Li J, Laack NN, Kruser TJ, Chmura SJ, Shi W, Deshmukh S, Mehta MP, Kachnic LA, for NRG Oncology: Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology CC001. J Clin Oncol 38(10): 1019-1029, 2020. DOI: 10.1200/JCO.19.02767

14 Sun Q, Li M, Wang G, Xu H, He Z, Zhou Y, Zhou Y, Zhou Y, Song H, Jiang H: Distribution of metastasis in the brain in relation to the hippocampus: a retrospective single-center analysis of 565 metastases in 116 patients. Cancer Imaging 19(1): 2, 2019. DOI: 10.1186/s40644-019-0188-6

15 Popp I, Rau S, Hintz M, Schneider J, Bilger A, Fennell JT, Heiland DH, Rothe T, Egger K, Nieder C, Urbach H, Grosu AL: Hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost for multiple brain metastases. Cancer 126(11): 2694-2703, 2020. DOI: 10.1002/cncr.32787

16 Kundapur V, Ellchuk T, Ahmed S, Gondi V: Risk of hippocampal metastases in small cell lung cancer patients at presentation and after cranial irradiation: a safety profile study for hippocampal sparing during prophylactic or therapeutic cranial irradiation. Int J Radiat Oncol Biol Phys 91(4): 781-786, 2015. DOI: 10.1016/j.ijrobp.2014.12.026

17 Kazda T, Jancalek R, Pospisil P, Sevela O, Prochazka T, Vrzal M, Burkon P, Slavik M, Hynkova L, Slampa P, Laack NN: Why and how to spare the hippocampus during brain radiotherapy: the developing role of hippocampal avoidance in cranial radiotherapy. Radiat Oncol 9: 139, 2014. DOI: 10.1186/1748-717X-9-139

18 Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, Khuntia D, Tomé WA: Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 78(4): 1244-1252, 2010. DOI: 10.1016/j.ijrobp.2010.01.039

19 Grosu AL, Frings L, Bentsalo I, Oehlke O, Brenner F, Bilger A, Fennell JT, Rothe T, Schneider-Fuchs S, Graf E, Schmoor C, Beck J, Becker G, Bock M, Egger K, Urbach H, Lahmann C, Popp I: Whole-brain irradiation with hippocampal sparing and dose escalation on metastases: neurocognitive testing and biological imaging (HIPPORAD) - a phase II prospective randomized multicenter trial (NOA-14, ARO 2015-3, DKTK-ROG). BMC Cancer 20(1): 532, 2020. DOI: 10.1186/s12885-020-07011-z

20 Megias D, Phillips M, Clifton-Hadley L, Harron E, Eaton DJ, Sanghera P, Whitfield G: Dose specification for hippocampal sparing whole brain radiotherapy (HS WBRT): considerations from the UK HIPPO trial QA programme. Br J Radiol 90(1071): 20160829, 2017. DOI: 10.1259/bjr.20160829

21 Kraft J, Weick S, Breuer K, Lutyj P, Bratengeier K, Exner F, Richter A, Tamihardja J, Lisowski D, Polat B, Flentje M: Treatment plan comparison for irradiation of multiple brain metastases with hippocampal avoidance whole brain radiotherapy and simultaneous integrated boost using the Varian Halcyon and the Elekta Synergy platforms. Radiat Oncol 17(1): 192, 2022. DOI: 10.1186/s13014-022-02156-6

22 van't Riet A, Mak AC, Moerland MA, Elders LH, van der Zee W: A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: Application to the prostate. Int J Radiat Oncol Biol Phys 37(3): 731-736, 1997. DOI: 10.1016/s0360-3016(96)00601-3

23 Yamashita M, Ohira S, Tanabe H, Kokubo M, Koizumi M: Correlation between dosimetric parameters and local control in definitive radiotherapy for head and neck cancers. In Vivo 38(2): 819-825, 2024. DOI: 10.21873/invivo.13506

24 Jones D: ICRU Report 50—Prescribing, recording and reporting photon beam therapy. Med Phys 21(6): 833-834, 1994. DOI: 10.1118/1.597396