



Dosimetric and radiobiological comparison of IMRT, VMAT, and helical tomotherapy planning techniques in hippocampal sparing whole brain radiotherapy with simultaneous integrated boost for multiple brain metastases

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Abstract

To compare treatment planning and dosimetric outcomes for hippocampal sparing whole brain radiotherapy (WBRT) with the simultaneous integrated boost (SIB) in brain metastasis (BM) patients using tumour control probability (TCP) and normal tissue complication probability (NTCP) formalism between IMRT, VMAT, and HT techniques. In this retrospective study, the treatment data of 20 BM patients who typically received whole brain radiation with SIB treatment were used. Prescription doses of 30 Gy and 36 Gy was delivered in 10 fractions for WBRT and SIB, respectively. Niemierko and LKB models were applied for calculating TCP and NTCP. All the plans were evaluated for the RTOG 0933 protocol criteria and found acceptable. Additionally, the homogeneity of the PTV boost is 0.07 ± 0.01 , 0.1 ± 0.04 , and 0.08 ± 0.02 for IMRT, VMAT, and HT, respectively ($P < 0.05$). The percentage of TCP for the PTV boost was 99.99 ± 0.003 , 99.98 ± 0.004 , and 99.99 ± 0.002 of IMRT, VMAT, and HT, respectively, ($P < 0.005$). The NTCP value of the lenses was higher with the VMAT plan as compared to IMRT and HT Plans. The hippocampal NTCP values are equal in all three planning proficiencies. The techniques like IMRT, VMAT, and HT can reduce the dose received by hippocampus to the dosimetric threshold during the delivery of WBRT with hippocampal sparing and can simultaneously boost multiple metastases. Overall, the high-quality dose distribution, TCP, and NTCP comparison between all three planning techniques show that the HT technique has better results when compared to the VMAT and IMRT techniques.

Keywords TCP · NTCP · Whole brain radiation · SIB · Hippocampal Sparing

Introduction

The prognosis for brain metastases (BM) is generally poor, with median survival rates ranging from one to a few years. Radiotherapy is an essential modality in the treatment of BM. However, neurocognitive deficit occurs due to both BM and radiotherapy (Garsa et al. 2021).

Whole brain radiotherapy (WBRT) is used as a primary treatment modality to treat multiple brain metastases and it may also be used as a stand-alone treatment for the

unresectable metastatic tumour. WBRT by parallel opposed fields is the standard palliative care for the BM and has a poor prognosis rate with survival rates of 3 to 6 months in many cases (Sundstrom et al. 1998). Advanced treatment modalities like intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and helical tomotherapy (HT) have highly conformal treatment delivery. These techniques can be used to deliver the whole brain treatment, and simultaneously a high dose can be delivered to the gross tumour volume (GTV) with minimal margins.

The hippocampus is a small structure in the brain and plays a significant role in the limbic system. The hippocampus supports the retrieval of stored memories and the formation of new memories. Bilateral or unilateral damage to the hippocampus is known to cause learning changes and memory formation. Several studies have demonstrated that whole brain radiation therapy causes a

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significant decline in the neurocognitive function (NCF) (Li et al. 2008; Pazzaglia et al. 2020). With the recent advancement in radiotherapy techniques, it is possible to have a WBRT with hippocampal sparing to avoid adverse effects.

The hippocampal avoidance whole brain radiotherapy is a technique that can reduce both the mean and maximum dose to the hippocampus for a prescription dose of 30 Gy in 10 fractions to the whole brain (Gondi et al. 2010a, b, c). In comparison to historical data of patients treated with regular WBRT, a phase II-RTOG0933 trial on hippocampal avoidance whole brain radiotherapy for brain metastases found considerable memory preservation (Gondi et al. 2014).

Tsai et al. (2015) investigated the correlation between hippocampal dosimetry and NCF outcomes in patients receiving HA-WBRT. The scores of NCFs were relatively stable before and after HS-WBRT in terms of hippocampus-dependent memory. Regarding verbal memory, the corresponding EQD2 values of 0, 10, 50, and 80% irradiating the composite hippocampal structure with < 12.60 Gy, < 8.81, < 7.45 Gy, and < 5.83 Gy, respectively, were significantly associated with neurocognitive preservation indicated by the immediate recall of Word List Test of Wechsler Memory Scale-III.

Sharma et al. (2021) compared the coplanar IMRT (C-IMRT), non-coplanar IMRT (NC-IMRT) and VMAT planning techniques in HS WBRT. They used nine coplanar fields with a couch angle of 0° for C-IMRT plans and all the NC-IMRT plans using nine non-coplanar beams without a collimator rotation and optimised couch angles depending on each patient's CT image. Four coplanar arcs were used for VMAT plans, closing less than half of the PTV region. All the plans achieved a hippocampus mean dose of less than 10 Gy, but the NC-IMRT and VMAT plans had superior target coverage and hippocampus sparing.

Yuen et al. (2020) performed an excellent study between the dual arc VMAT (dac-VMAT) and split arc and partial field VMAT (sopf-VMAT) planning techniques in HA-WBRT for a cohort of 20 patients. They have used four partial arcs in the sopf-VMAT and two full arcs in the dac-VMAT techniques. The D100% of the hippocampus dose was 9.23 Gy and 7.86 Gy with dac-VMAT and sopf-VMAT, respectively. Also, they found a significant dose reduction in sopf-VMAT to the hippocampus and eyes compared to dac-VMAT.

Chen et al. (2021) compared coplanar VMAT (C-VMAT) and non-coplanar VMAT (NC-VMAT) techniques with a cohort of 9 patients of HA-WBRT. They used four full arcs in coplanar plans for C-VMAT and four full arcs plus one non-coplanar arc in NC-VMAT techniques. The hippocampus doses of D100% were 8.6 Gy, 8.56 Gy and Dmax of 15.29 Gy and 14.99 Gy for C-VMAT and NC-VMAT techniques, respectively. Even though the OAR doses are less in

the NC-VMAT techniques, the overall treatment was higher with this technique.

Ishibashi et al. (2021) studied the modulation factor's (MF's) influence on the treatment plan quality and treatment time in the HT technique in HA-WBRT. The variable plans have different MF values of 3.0, 2.6, 2.2, 1.8 and 1.4, a standard pitch value of 0.2 and a field width of 1 cm used for the analysis. The reduction in MF shows a gradual reduction in the treatment time, but the PTV coverage was poor if the MF was less than 1.8 during the sparing of the hippocampus. The HT plans can yield better HA-WBRT plans with the MF from 3 to 1.8.

Yokoyama et al. (2022) compared the plan quality between the Halcyon and HT planning techniques in HA-WBRT. The Halcyon plan with 1 to 4 arcs was compared with the HT plan to analyse the hippocampus dose. The hippocampus sparing was better with the 3 and 4 arcs (Dmax < 15 Gy) compared to 1 arc (Dmax < 18 Gy) and two arcs (Dmax < 16 Gy) with the halcyon plan. The HT plan shows significant hippocampus sparing compared (Dmax < 12 Gy) to the Halcyon plan with 3 and 4 arcs, but the treatment time of the HT plan was higher than that of the Halcyon plan.

Modern RT techniques such as dynamic IMRT, VMAT, and HT can produce steep dose gradients between OAR and the target volume. Also, differential doses to the whole brain and brain metastases can be given simultaneously with these techniques. The simultaneous integrated boost (SIB) method offers enhanced patient comfort due to an optimised dose distribution, reducing overall treatment time and expenses when compared to the sequential boost method. The dose heterogeneity for the whole brain volume increases by sparing the hippocampus whilst simultaneously boosting the dose to metastases.

The aim of this study was to compare dosimetric and radiobiological parameters for modern radiotherapy techniques, such as IMRT, VMAT and HT in whole brain radiotherapy with simultaneous integrated boost with hippocampal sparing in multiple brain metastases.

Materials and methods

Patient selection and imaging

The treatment data of 20 patients (14 male and six female) (aged between 43 and 86 years, mean 66.5 years) who received treatment for multiple brain metastases ranging from 1 to 17 have been used in this study. All patients were simulated with all-in-one (AIO) solutions in the head-first supine position. A three-clamp thermoplastic mask was prepared to immobilise the patients. A kilovoltage computed tomography (CT) scan with a slice thickness of 1.25

to 2.5 mm was acquired from the vertex to C5 vertebra to include the whole brain volume. Contrast-enhanced magnetic resonance imaging (CEMRI) was registered to the planning CT images to delineate gross tumour volume (GTV) and organ at risk (OAR) structures.

The RTOG 0933 contouring atlas was used as a guideline to define the targets and organs at risk (OARs) in an eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA). With the help of MRI and CT co-registered images, the gross tumour volumes (GTVs) and bilateral hippocampus were accurately contoured. The boost planning target volume (PTV boost) was created from GTVs using a 2 mm isotropic margin. The hippocampus avoidance (HA) zone was created using a margin of 5 mm from the hippocampus. The clinical target volume (CTV) has been created by delineating the entire brain. The whole brain planning target volume (PTV) was created from CTV using a 3 mm isotropic margin and cropping from the HA and boost volume. OARs such as optic nerve, optic chiasm, brain stem, eye, lens, pituitary, parotid, and spinal cord were created for planning comparison. Additionally, three-ring structures were created by applying 3 mm, 4 mm, and 1 cm margins from the total-hippocampus structure to achieve conformity in the whole brain PTV dose coverage. The PTV volumes, the number of boost volumes of individual patients, and the distance

between boost volume and hippocampus are mentioned in Table 1.

Treatment planning

We have used eleven fields with nine coplanar equally spaced from 200 to 160 degree (collimator 90-degree, couch 0-degree) and two non-coplanar fields 310 and 335 degree (collimator 0-degree, couch 90-degree). We have used total four coplanar fields with two clock wise (CW 180.1–179.9, collimator rotation 85 degree) and two counter clockwise (CCW 179.9–180.1, collimator rotation 95 degree) as mentioned in Table 2. The field projection for IMRT and VMAT were displayed in axial and 3D view in Fig. 1.

All plans were optimised with an aggregate dose of 30 Gy for PTV whole brain and simultaneously 36 Gy for PTV boost in 10 fractions using three planning proficiencies (HT, IMRT, and VMAT). The Eclipse treatment planning system (version 15.6, Varian, USA) has data configured for the 6 MV photon energy Varian TrueBeam accelerator, with an HD 120 Multi-Leaf Collimator (MLC) with 60 leaf pairs (with a spatial resolution of 0.25 cm in the centre and 0.5 cm in the periphery), had been used to create the VMAT and IMRT plans. An Anisotropic Analytical Algorithm (AAA) dose calculation model was used to calculate the dose after setting the calculation grid size to 2.5 mm. The optimization

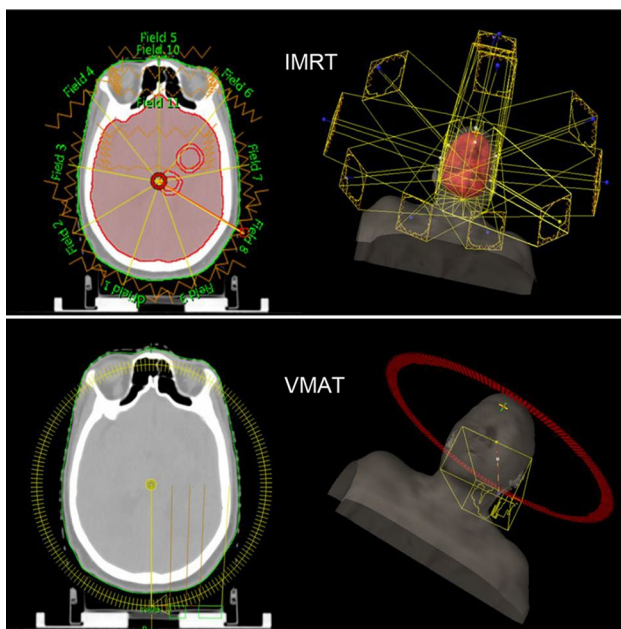
Table 1 Patient wise OAR and PTV characteristics

Patient	No of boost volume	PTV boost Volume (CC)	Hippocampus volume (CC)	Minimum distance between boost volume and hippocampus (mm)	PTV whole brain volume (CC)
1	1	29.4	4.1	41	1239.7
2	10	212.8	6.8	10	1224.2
3	6	25.2	2.9	1	1336.8
4	3	97.3	6.6	10	1335.5
5	1	71.4	1.7	21	1270.7
6	2	143.1	1.4	6	1242.4
7	3	63.4	1.9	8	1734.1
8	1	103.1	10.8	10	1727.3
9	1	49.5	1.8	44	1375.1
10	17	30.2	3.2	5	1319.1
11	3	54.0	2.9	36	1443.6
12	2	10.3	2.2	20	1934.5
13	1	54.4	2.6	12	1601.2
14	3	33.3	3.4	16	1476.2
15	4	48.9	3.2	6	1331.1
16	2	18.5	2.0	50	1383.5
17	2	5.7	1.5	8	1801.9
18	5	117.3	4.6	14	1453.9
19	2	21.1	3.9	6	1426.8
20	1	24.6	2.4	56	1326.3

OAR Organ at Risk, PTV Planning Target Volume

Table 2 IMRT and VMAT plan gantry, collimator and couch parameters

Field number	IMRT Gantry Angle (degree)	IMRT Collimator angle (degree)	IMRT Couch angle (degree)	VMAT Gantry Angle (degree)	VMAT Collimator angle (degree)	VMAT Couch angle (degree)
Field1	200	90	0	180.1CW179.9	85	0
Field2	240	90	0	180.1CW179.9	85	0
Field3	280	90	0	179.9CCW180.1	95	0
Field4	320	90	0	179.9CCW180.1	95	0
Field5	0	90	0	–	–	–
Field6	40	90	0	–	–	–
Field7	80	90	0	–	–	–
Field8	120	90	0	–	–	–
Field9	160	90	0	–	–	–
Field10	310	0	90	–	–	–
Field11	335	0	90	–	–	–

**Fig. 1** IMRT and VMAT field Projection

objectives for IMRT and VMAT were not modified between individual patients to avoid introducing bias in the planning. However, due to the difference in the treatment planning system (Precision) for HT plans, the optimization objectives did not match the IMRT and VMAT plans, as shown in Fig. 2.

The CT images and structure datasets were transferred to the precision workstation (version 3.3, precision, Accuray, USA) database via the DICOM RT protocol to create a HT plans. The field width of 2.5 cm, modulation factor of 3, and the pitch value of 0.3 are the parameters used for optimization in the treatment planning workstation. A Radixact machine (Version X9, Accuray, USA) was selected as a treatment machine with 6 MV flattening filter-free photon

energy with a dynamic jaw (Tomo edge) and 0.625 cm resolution binary MLC in the treatment planning system. The final dose calculation has been performed using the collapsed cone convolution superposition (CCCS) algorithm for HT plans.

We followed the RTOG 0933 planning criteria mentioned in Table 3 in all three planning methods for whole brain PTV with hippocampal avoidance. The dose coverage of 95% of the target volume was covered with at least 95% of the prescription dose to boost volume. The PTV boost volume dose coverage was not compromised even though the boost volume falls near or inside the hippocampal avoidance region. Also, the optimization process was repeated until the OAR doses could be further reduced without compromising PTV coverage for all three techniques.

Dosimetric plan quality comparison

Target coverage analysis

The coverage of the PTV whole brain was analysed by V30Gy (Volume covered by 30 Gy isodose line), D2% (Dose received by 2% of PTV volume), and D98% (Dose received by 98% of PTV volume) as mentioned in Table 3. The PTV boost was analysed for D98% (Dose received by 98% of PTV volume), and the PTV whole brain and PTV boost were evaluated for their conformity index, coverage index, and homogeneity index (Table 4) to identify and compare the plan quality.

Organ at risk analysis

The hippocampus dose was evaluated with maximum dose (Dmax), mean dose (Dmean), and D100% (Dose in 100% of volume). All other OARs like optic chiasm, brain stem,

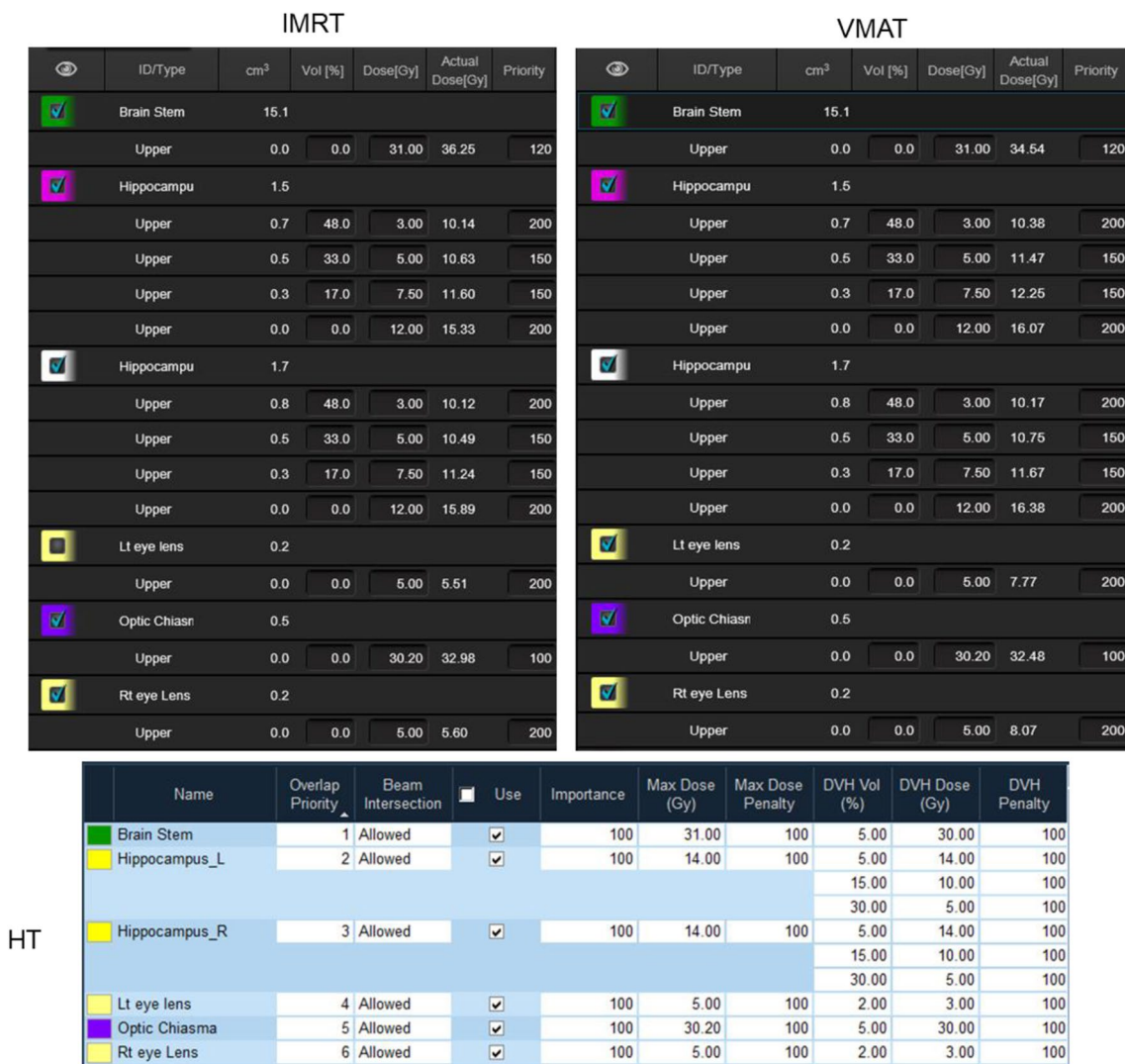


Fig. 2 Optimization objectives for major organs for IMRT, VMAT and HT plans

Table 3 Dose volume criteria of RTOG 0933 (Cui et al. 2013)

PTV/OAR	Criteria	Variation acceptable	Variation unacceptable
PTV whole brain volume	$D_{2\%} \leq 37.5$ Gy	$D_{2\%} \leq 40$ Gy	$V_{30Gy} < 90\%$
	$D_{98\%} \geq 25$ Gy	$D_{98\%} < 25$ Gy	$D_{2\%} > 40$ Gy
Bilateral-Hippocampus	$D_{100\%} \leq 9$ Gy	$D_{100\%} \leq 10$ Gy	$D_{100\%} > 10$ Gy
	$D_{max} \leq 16$ Gy	$D_{max} \leq 17$ Gy	$D_{max} \geq 17$ Gy
Optic Nerves and Optic Chiasm ^a	$D_{max} \leq 37.5$ Gy	$D_{max} \leq 37.5$ Gy	$D_{max} \geq 37.5$ Gy

^aDmax is dose to 0.03 cc volume of the organ at risk, D2%-Dose received by 2% of volume, D98%-Dose received by 98% of the volume, D100%-Dose received by 100% of the volume, Dmax-Maximum dose, V30Gy-volume covered by 30 Gy isodose line

combined parotid, optic nerve, lens, and eye (Left & Right) doses were evaluated for Dmax and Dmean.

Radiobiological analysis

The TCP of both PTV whole brain and boost volume have been analysed with Niemierko’s EUD model (Table 4) with the parameters $TCD50 = 22.17$ Gy, $\gamma50 = 3.6$,

Table 4 Dosimetric and radiobiological equations for the plan comparison

Name	Equations	Parameters required	References
Conformity index	$CI = \frac{\text{Volume } 95\% \text{ of } PD}{PTV \text{ Vol}}$	PD = prescription dose to the PTV PTV Vol = total PTV volume	(Feuvret et al. 2006)
Homogeneity index	$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$	$D_{98\%}$ = dose received by 98% of PTV $D_{2\%}$ = dose received by 2% of PTV $D_{50\%}$ = dose received by 50% of PTV	
Coverage Index	$Cov \ 1 = \frac{D_{min}}{PD}$	D_{min} = minimum dose received by PTV PD = prescription dose received by PTV	
Equivalent Uniform Dose (EUD)	$EUD = \left(\sum_{i=1} V_i EQD_i^a \right)^{1/a}$ $EQD_i = D_i \cdot \frac{\left(\frac{\alpha}{\beta} + \frac{D_i}{nf} \right)}{\left(\frac{\alpha}{\beta} + 2 \right)}$	EQD_i = dose delivered to a sub volume V_i a = unitless model parameter D_i = total dose received by the bin nf = total number of fractions α/β = parameters of the linear-quadratic model	(Niemierko 1999; Gay and Niemierko 2007)
Niemierko's TCP and NTCP model	$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD} \right)^{4\gamma_{50}}}$ $NTCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD} \right)^{4\gamma_{50}}}$	γ_{50} = a unit less model parameter describing the dose–response curve's slope TCD50 = tolerance dose needed for controlling 50% of the tumour (if irradiated uniformly) TD50 = tolerance dose to produce 50% of complication of OARs (if uniformly irradiated) V_i = volume in a specific dose bin i D_i = dose given to each bin	(Gay and Niemierko 2007; Sohn et al. 2007)
Lyman–Kutcher–Burman (LKB) model	$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx$ $t = \frac{D_{eff} - TD_{50}}{m \cdot TD_{50}}$ $D_{eff} = \left(\sum_i V_i D_i^{\frac{1}{n}} \right)^n$	TD50 = tolerance dose to produce 50% of complication of OARs (if uniformly irradiated) V_i = volume in a specific dose bin i D_i = dose given to each bin m = dimensionless parameter for determining the slope of complication probability versus dose curve n = volume dependence of the complication's probability	(Lyman and Wolbarst 1987; Kutcher et al. 1991; Okunieff et al. 1995)

Table 5 Parameters used for NTCP calculations (Okunieff et al. 1995; Emami et al. 1991)

Organ	n	m	TD ₅₀ (Gy)	α/β	End point
Brain Stem	0.16	0.14	65	3	Necrosis
Lens ^a	0.3	0.27	18	1.2	Blindness
Eye ^a	0.2	0.19	65	3	Blindness
Optic nerve ^a	0.25	0.14	65	3	Blindness
Parotid ^a	0.7	0.18	28.4	3	Xerostomia
Hippocampus ^a	0.25	0.15	48	2	NCF decline

^aBoth left and right side

NCF neurocognitive function

$a = -1$, and $\alpha/\beta = 10$ (Kendall et al. 2008). The OARs have been analysed with LKB model (Table 4) with the parameters mentioned in Table 5.

Statistical analysis

Data are shown as mean [\pm] standard deviation (SD). Radiobiological metrics and differences in the dosimetric parameters amongst the three plans have been analysed with a 2 tailed student t-test (IBM, SPSS_v24). A p-value of less than 0.05 was regarded as statistically significant.

Results

All the plans were evaluated based on the RTOG 0933 protocol criteria (Table 3) and found acceptable. Additionally, the homogeneity of the PTV boost was 0.07 ± 0.01 , 0.1 ± 0.04 , and 0.08 ± 0.02 for IMRT, VMAT, and HT, respectively (Table 6), and the comparison between the plans was statistically significant ($P < 0.05$). The percentage of volume covered by 30 Gy dose to PTV whole brain was 92.5 ± 1.62 , 92.04 ± 1.85 , and 91.68 ± 1.87 for IMRT, VMAT, and HT,

Table 6 Dosimetric comparison of planning target volume

Parameters	IMRT ⁽ⁱ⁾		VMAT ^(j)		HT ^(k)		P -Value			
	Mean	SD	Mean	SD	Mean	SD	I vs j	I vs k	j vs k	
PTV boost	Dmax (Gy)	39.32	0.92	39.20	1.22	39.81	0.86	0.73	0.08	0.07
	Dmean (Gy)	37.78	0.71	36.61	0.54	37.75	0.39	0.00	0.85	0.00
	HI	0.07	0.01	0.10	0.04	0.08	0.02	0.00	0.02	0.02
	CI	1.00	0.00	0.99	0.02	1.00	0.01	0.10	0.58	0.10
	Cov I	0.95	0.10	0.95	0.11	0.93	0.11	0.88	0.36	0.37
PTV whole brain	D30Gy (%)	92.50	1.62	92.04	1.85	91.68	1.87	0.31	0.17	0.46
	D2% (Gy)	34.23	0.82	34.97	0.62	33.83	0.53	0.00	0.08	0.00
	D98% (Gy)	26.38	1.08	26.63	0.72	26.28	0.68	0.35	0.74	0.04
	HI	0.25	0.04	0.26	0.03	0.24	0.03	0.31	0.69	0.02
	CI	0.96	0.01	0.96	0.01	0.96	0.01	0.59	0.13	0.30
	Cov I	0.47	0.08	0.47	0.05	0.45	0.13	0.81	0.00	0.64
V90% (%)	97.42	0.90	97.70	0.59	97.64	0.33	0.36	0.23	0.59	

IMRT Intensity modulated radiotherapy, *VMAT* Volumetric modulated arc therapy, *HT* Helical tomotherapy, *PTV* Planning target volume, *Dmax* maximum dose to the PTV, *Dmin* minimum dose to the PTV, *Dmean* mean dose to the PTV, *CI* Conformity Index, *HI* Homogeneity index, *Cov I* Coverage Index, *V90%* 90% of dose covered by the percentage of PTV volume, *D2%* Dose received by 2 percentage of volume, and *D98%* Dose received by 98 percentage of volume

respectively. The differences between the plans were not statistically significant. The parameters of PTV boost and PTV whole brain are mentioned in Table 6. The PTV boost and PTV whole brain dose coverage for all three plans for patient number 10 are shown in Fig. 3.

The dose to the 100% of volume (D100%) received by both left and right-side hippocampi is displayed in Fig. 4, and it shows that HT plans received fewer doses compared to IMRT and VMAT plans. D100% of all three plans adhered to the RTOG protocol values mentioned in Table 3.

The distance between the hippocampus is less than 1 cm from the PTV boost, also more than three PTV boost volume patients, a total of eleven patients were separately analysed for the maximum hippocampus dose (Fig. 5). Four patients had a higher maximum hippocampus dose when the distance was less between the PTV boost and the hippocampus compared with IMRT and VMAT plans.

The equivalent uniform dose (EUD) of the OARs like parotid, hippocampus, brain stem, and spinal cord are mentioned in Table 7. The mean parotid dose of the left and right side, brain stem, and spinal cord are less for HT plans as compared to IMRT and VMAT plans. The difference between plans (IMRT versus HT) and (VMAT versus HT) is statistically significant ($P < 0.05$) for parotid. Also, the comparison between (IMRT versus VMAT) and (VMAT versus HT) is statistically significant ($P < 0.05$) for hippocampus and brainstem.

The comparison between equivalent uniform doses for optic structures like the eye, lens, optic chiasm, and optic nerve are shown in Fig. 6. The HT plan doses for optic structures are less than IMRT and VMAT plans, except for optic

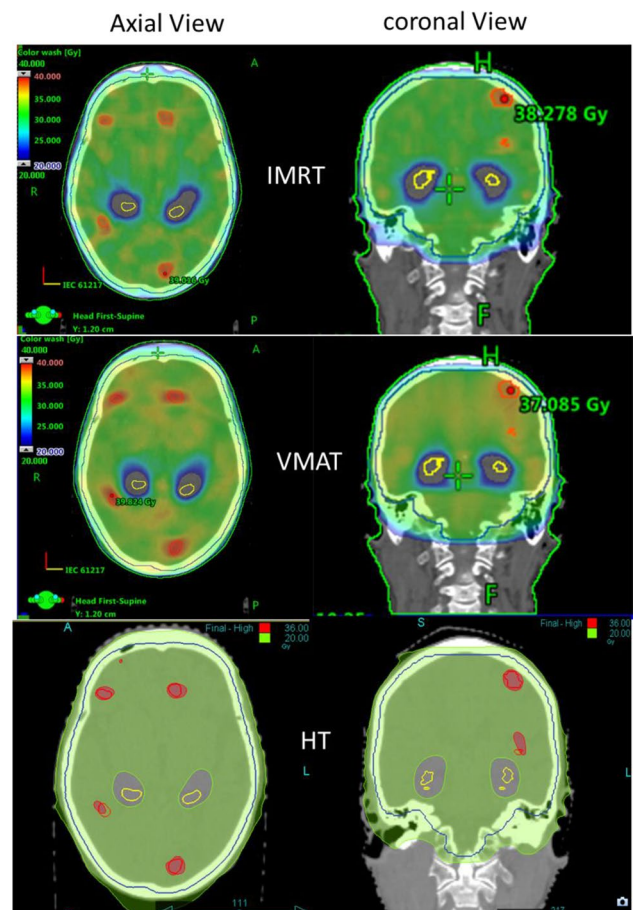


Fig. 3 Dose coverage of PTV boost with 36 Gy and PTV whole brain with 30 Gy on axial and coronal view for IMRT, VMAT, and HT plans

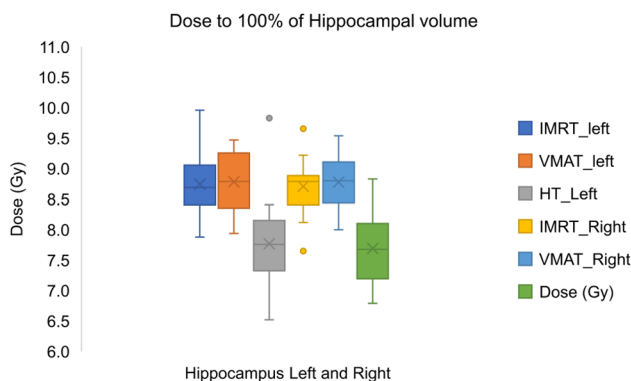


Fig. 4 Dose to 100% of left and right hippocampal volume

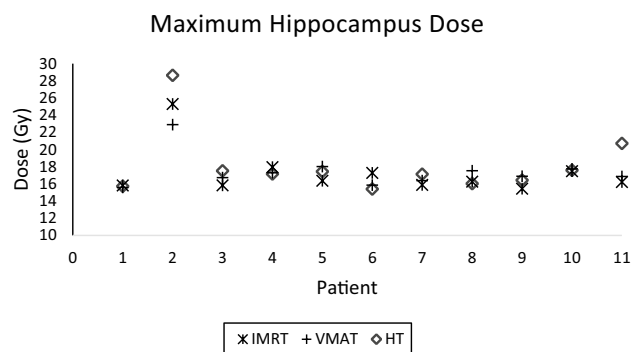


Fig. 5 Maximum dose to hippocampus for the patients with more than three PTV boost volume and distance between hippocampus and PTV boost volume less than 1 cm

chiasm. Also, the optic structures receive higher doses by the VMAT plan when compared to the IMRT plan, except for the eye.

Figure 7 shows the comparison of the equivalent uniform dose of hippocampal left and right sides. The average EUD of the left and right hippocampus were 8.01 Gy ± 0.65, 8.74 Gy ± 0.66, 8.31 Gy ± 1.0, 8.14 Gy ± 0.59, 8.68 Gy ± 0.50, and 7.99 Gy ± 0.61 for IMRT, VMAT, and HT plans, respectively. The mean dose for the left-sided hippocampus was higher in the HT plan compared to the IMRT and VMAT. Also, the left-sided hippocampal doses were

higher for patient number 3 on all three planning proficiencies, 9.76 Gy, 10.79 Gy, and 12.28 Gy for IMRT, VMAT, and HT, respectively. These doses were higher because the location of the PTV boost volume was within 5 mm of the left hippocampus.

The TCP of the PTV boost were 99.99% ± 0.003, 99.98% ± 0.004, and 99.99% ± 0.002 of IMRT, VMAT, and HT, respectively, and the comparison between IMRT versus VMAT and VMAT versus HT are statistically significant (P < 0.005). Also, the TCP of PTV whole brain was 92.42% ± 11.86, 97.24% ± 3.6, and 93.98% ± 3.8 for IMRT, VMAT, and HT, respectively, and the comparison between the plans is not statistically significant.

The NTCP of the OARs was evaluated with the LKB model, and found that the HT plans have lesser value compared to IMRT and VMAT plans, except for optic chiasm. The NTCP value of the left and right lenses were higher with the VMAT plan compared to IMRT and HT Plans. The hippocampal NTCP values are equal in all three planning proficiencies, and the NTCP value is higher for the brain stem and spinal cord in the IMRT plan when compared to VMAT and HT plans (Fig. 8).

Discussion

The IMRT, VMAT, and HT are techniques with well-established roles for hippocampal sparing in whole-brain radiation therapy. The study result of Gondi et al. shows that 87% and 81% of hippocampal doses can be saved using HT and LINAC-based IMRT techniques, respectively. The authors also commented that it is challenging to spare the hippocampus whilst delivering a simultaneous boost with whole-brain irradiation (Gondi et al. 2010a, b, c).

Recently, Popp et al. (2021) conducted a study comparing WBRT and HA-WBRT techniques for a cohort of 48 and 35 patients, respectively. The results showed an average atrophy of 3.1% with HA-WBRT compared to 8.5% with conventional WBRT in the first two years after radiotherapy.

We have studied the possibility of sparing the hippocampus and other OARs whilst performing the WBRT and simultaneous boost with three planning methods and

Table 7 Equivalent uniform dose for organ at risk

Name	IMRT ⁽ⁱ⁾		VMAT ^(j)		HT ^(k)		P -Value		
	Mean	SD	Mean	SD	Mean	SD	i Vs j	i Vs k	j Vs k
Parotid Rt	8.90	2.96	9.27	3.34	4.34	0.82	0.18	0.00	0.00
Parotid Lt	8.69	2.52	8.66	3.25	4.17	0.77	0.94	0.00	0.00
Total Hippocampal	8.09	0.63	8.73	0.58	8.22	0.78	0.00	0.40	0.00
Brain Stem	38.94	1.96	37.36	3.47	38.70	1.81	0.04	0.67	0.02
Spinal cord	30.66	7.79	28.27	8.59	28.95	8.32	0.02	0.08	0.30

IMRT Intensity modulated radiotherapy, VMAT Volumetric modulated arc therapy, HT Helical tomotherapy

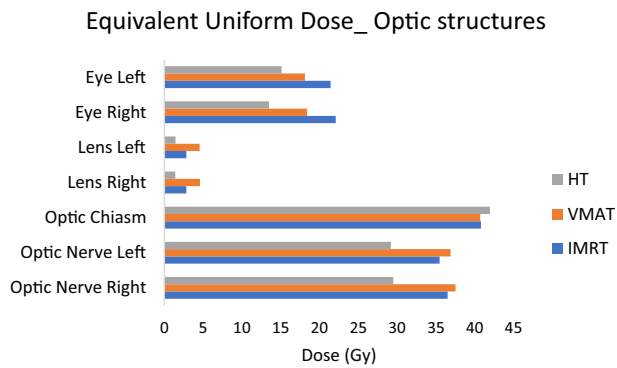


Fig. 6 Equivalent uniform dose of optic structures

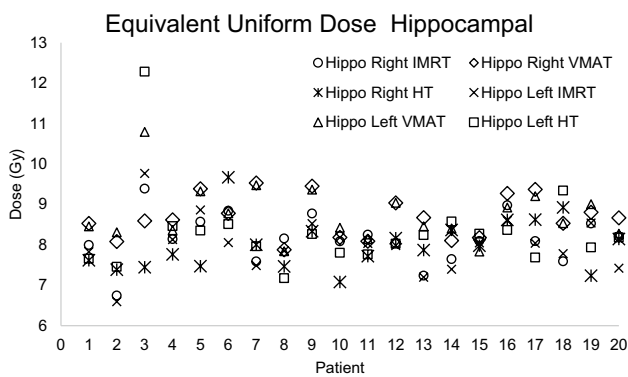


Fig. 7 Equivalent uniform dose of left and right hippocampus

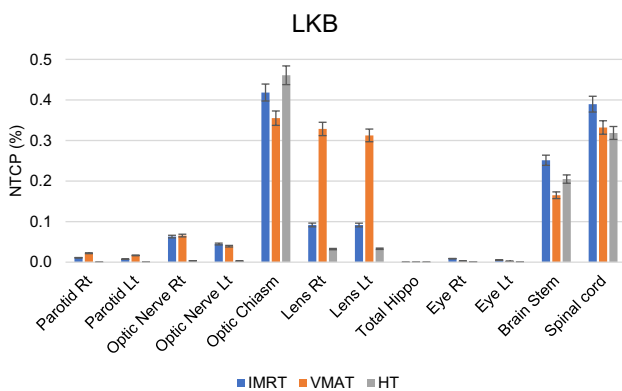


Fig. 8 Normal tissue complication probability of the organ at risk

compared these plans with dosimetric, EUD, and radiobiological models. Balasubramanian and Shobana (2021; 2022) compared photon and proton planning radiobiologically using LKB and Niemierko NTCP models, and they found that the results were reliable for comparing different planning methods.

The use of the HT delivery technique for hippocampal avoidance of WBRT with SIB has been investigated by

Gutierrez et al. (2007). Also, they compared dosimetric parameters of different treatment plans as a function of the field width (FW) and pitch value. They found that smaller FW can improve the homogeneity to the WBRT and reduce mean eye dose. Also, the mean dose to the hippocampus was unchanged amongst the different pitch values and FW.

Hus et al. (2010) studied the VMAT delivery technique for hippocampal avoidance of WBRT with SIB in patients with one to three metastases. They discovered that the VMAT technique could deliver WBRT efficiently whilst conformally limiting the hippocampus dose and simultaneously delivering radio surgical equivalent doses to selected metastases. Gondi et al. (2010a, b, c) addressed the problem of hippocampus avoidance during WBRT in a comprehensive hypothesis paper. They found that the risk of therapeutic failure due to relapse or progression in the hippocampus subgranular zone, however, is still a significant issue.

Preclinical research suggests that radiation-induced cognitive impairment following cranial irradiation is due to the dose received by the neural stem cell (NSC) compartment in the hippocampus dentate gyrus. In a prospective observational study of adult patients with benign or low-grade brain tumours treated with fractionated stereotactic radiation, the authors identified a dosage association between EQD2 to bilateral hippocampi and the chance of long-term memory impairment. An EQD2 to 40% of the bilateral hippocampi (D40%) greater than 7.3 Gy predicts cognitive impairment after 18 months of follow-up (Gondi et al. 2012).

Our study showed outstanding target coverage with good dose homogeneity for the boost volume, achieved 25 Gy coverage to the D98% of whole brain volume, and favourable normal tissue sparing with the HT plan compared with other techniques. The higher hippocampal dose was noted in some patients, possibly due to the boost volume near the hippocampus. The NTCP of the optic structure was low with all the planning proficiencies except optic chiasm.

Our study has certain limitations like that the planning system and algorithm used for calculations could have an impact on the results. The NTCP values in this study were estimated using radiobiological models which did not consider tumour cell repopulation and oxygenation during the treatment course. Lastly, not all plans used the reference standard Monte Carlo (MC) for calculation.

Conclusion

The techniques like IMRT, VMAT, and HT can reduce the dose received by the hippocampus to the dosimetric threshold in hippocampal avoidance WBRT with a simultaneous boost to selected metastases. The reduction in dosage to the OARs is also possible in all these three planning proficiencies. The planning could be ranked and compared based on

the anatomical and clinical challenges of each patient, using dosimetric parameters with the TCP and NTCP estimated radiobiological parameters. Overall, the high-quality dose distribution, TCP, and NTCP comparison between all three planning techniques show that the HT technique yields better results when compared to VMAT and IMRT techniques.

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Data availability Data will be available on request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest with respect to the manuscript.

Ethical approval Institutional scientific and Ethics Committee has approved this study. This article does not contain any studies with human participants performed by any of the authors.

References

- Balasubramanian S, Shobana MK (2021) Pediatric craniospinal Irradiation-the implementation and use of normal tissue complication probability in comparing photon versus proton planning. *J Med Phys* 46(4):244–252. https://doi.org/10.4103/jmp.jmp_75_21
- Balasubramanian S, Shobana MK (2022) A dosimetric and radiobiological comparison of intensity modulated radiotherapy, volumetric modulated arc therapy and helical tomotherapy planning techniques in synchronous bilateral breast cancer. *Asian Pac J Cancer Prev* 23(12):4233–4241. <https://doi.org/10.31557/APJCP.2022.23.12.4233>
- Chen L, Li M, Cheng H, Kuo C, Sun W, Tsai J (2021) Hippocampus-sparing whole-brain radiotherapy: dosimetric comparison between non-coplanar and coplanar planning. *Therapeutic Radiol Oncol*. <https://doi.org/10.21037/tro-20-50>
- Cui Y, Gondi V, Mehta MP, Manfredi D, Galvin JM, Xiao Y, Tomé W (2013) Credentialing in Hippocampal (HC) Sparing techniques for RTOG 0933: Quality Assurance (QA) Report. *Int J Radiat Oncol Biol Phys* 87(2):S576. <https://doi.org/10.1016/j.ijrobp.2013.06.1527>
- Emami B, Lyman J, Brown A (1991) Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 21:109–122. [https://doi.org/10.1016/0360-3016\(91\)90171-y](https://doi.org/10.1016/0360-3016(91)90171-y)
- Feuvret L, Noël G, Mazeron JJ, Bey P (2006) Conformity index: a review. *Int J Radiat Oncol Biol Phys* 64(2):333–342. <https://doi.org/10.1016/j.ijrobp.2005.09.028>
- Garsa A, Jang JK, Baxi S, Chen C, Akinniranye O, Hall O, Larkin J (2021) Radiation therapy for brain metastases: a systematic review. *Pract Radiat Oncol* 11(5):354–365. <https://doi.org/10.1016/j.prro.2021.04.002>
- Gay HA, Niemierko A (2007) A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. *Physica Medica PM Int J Devot Appl Phys Med Biol: off J Ital Assoc Biomed Phys* 23(3–4):115–125. <https://doi.org/10.1016/j.ejmp.2007.07.001>
- Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, Khuntia D, Tomé WA (2010a) 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. <https://doi.org/10.1016/j.ijrobp.2010.01.039>
- Gondi V, Tome WA, Marsh J, Struck A, Ghia A, Turian JV, Bentzen SM, Kuo JS, Khuntia D, Mehta MP (2010b) Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: safety profile for RTOG 0933. *Radiother Onco* 195(3):327–331. <https://doi.org/10.1016/j.radonc.2010.02.030>
- Gondi V, Tomé WA, Mehta MP (2010c) Why avoid the hippocampus? A comprehensive review. *Radiother Oncol* 97(3):370–376. <https://doi.org/10.1016/j.radonc.2010.09.013>
- Gondi V, Hermann BP, Mehta MP, Tomé WA (2012) Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys* 83(4):e487–e493. <https://doi.org/10.1016/j.ijrobp.2011.10.021>
- Gondi V, Pugh SL, Tomé WA, Caine C, Corn B et al (2014) 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. <https://doi.org/10.1200/JCO.2014.57.2909>
- Gutiérrez AN, Westerly DC, Tomé WA, Jaradat HA, Mackie TR et al (2007) Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. *Int J Radiat Oncol Biol Phys* 69(2):589–597. <https://doi.org/10.1016/j.ijrobp.2007.05.038>
- Hsu F, Carolan H, Nichol A, Cao F, Nuraney N et al (2010) Whole brain radiotherapy with hippocampal avoidance and simultaneous integrated boost for 1–3 brain metastases: a feasibility study using volumetric modulated arc therapy. *Int J Radiat Oncol Biol Phys* 76(5):1480–1485. <https://doi.org/10.1016/j.ijrobp.2009.03.032>
- Ishibashi A, Kurosaki H, Miura K, Utsumi N, Sakurai H (2021) Influence of modulation factor on treatment plan quality and irradiation time in hippocampus-sparing whole-brain radiotherapy using tomotherapy. *Technol Cancer Res Treat* 20:1533033821104549. <https://doi.org/10.1177/15330338211045497>
- Kendall E, Algan O, Ahmad S (2008) Comparison of Volumetric modulated arc therapy and intensity modulated radiation therapy for whole brain hippocampal sparing treatment plans based on radiobiological modeling. *J Med Phys* 43(1):16–22. https://doi.org/10.4103/jmp.JMP_85_17
- Kutcher G, Burman C (1989) Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. *Int J Radiat Oncol Biol Phys* 16:1623–1630. [https://doi.org/10.1016/0360-3016\(89\)90972-3](https://doi.org/10.1016/0360-3016(89)90972-3)
- Kutcher G, Burman C, Brewster L (1991) Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys* 21:137–146. [https://doi.org/10.1016/0360-3016\(91\)90173-2](https://doi.org/10.1016/0360-3016(91)90173-2)
- Li J, Bentzen SM, Li J, Renschler M, Mehta MP (2008) Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 71(1):64–70. <https://doi.org/10.1016/j.ijrobp.2007.09.059>

- Lyman JT, Wolbarst AB (1987) Optimization of radiation therapy: a method of assessing complication probabilities from dose-volume histograms. *Int J Radiat Oncol Biol Phys* 13:103–109. [https://doi.org/10.1016/0360-3016\(87\)90266-5](https://doi.org/10.1016/0360-3016(87)90266-5)
- Niemierko A (1999) A generalized concept of equivalent uniform dose (EUD). *Med Phys* 26:1100
- Yokoyama K, Kurosaki H, Oyoshi H, Miura K, Utsumi N (2022) Plan quality comparison between hippocampus-sparing whole-brain radiotherapy treated with halcyon and tomotherapy intensity-modulated radiotherapy. *Technol Cancer Res Treat* 21:15330338221108528. <https://doi.org/10.1177/15330338221108529>
- Okunieff P, Morgan D, Niemierko A, Suit HD (1995) Radiation dose-response of human tumors. *Int J Radiat Oncol Biol Phys* 32(4):1227–1237. [https://doi.org/10.1016/0360-3016\(94\)00475-z](https://doi.org/10.1016/0360-3016(94)00475-z)
- Pazzaglia S, Briganti G, Mancuso M, Saran A (2020) Neurocognitive decline following radiotherapy: mechanisms and therapeutic implications. *Cancers (Basel)* 12(1):146. <https://doi.org/10.3390/cancers12010146>
- Popp I, Rau A, Kellner E, Reiser M, Fennell JT et al (2021) Hippocampus-avoidance whole-brain radiation therapy is efficient in the long-term preservation of hippocampal volume. *Front Oncol* 11:714709. <https://doi.org/10.3389/fonc.2021.714709>
- Sharma AV, Bagdare P, Chadha P, Shree P, Gupta M, Chauhan R, Jaiswal I, Talapatra K (2021) Dosimetric comparison of coplanar intensity-modulated radiotherapy, noncoplanar intensity-modulated radiotherapy, and volumetric arc therapy planning technique in hippocampal-sparing whole-brain radiotherapy. *Radiat Prot Environ* 44(1):22–27. https://doi.org/10.4103/rpe.rpe_48_20
- Sohn M, Yan D, Liang J (2007) The incidence of late rectal bleeding in high-dose conformal radiotherapy of prostate cancer using EUD-and Dose-Volume Based NTCP models. *Int J Radiat Oncol Biol Phys* 67:1066. <https://doi.org/10.1016/j.ijrobp.2006.10.014>
- Sundstrom JT, Minn H, Lertola KK, Nordman E (1998) Prognosis of patients treated for intracranial metastases with whole-brain irradiation. *Ann Med* 30(3):296–299. <https://doi.org/10.3109/07853899809005858>
- Tsai PF, Yang CC, Chuang CC et al (2015) Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. *Radiat Oncol* 10:253. <https://doi.org/10.1186/s13014-015-0562-x>
- Wang D, Ma X, Fu L, Gu J, Bai T, Yin Y, Li B, Zhu J (2021) The Capabilities and characteristics of helical tomotherapy and co-planar dual arcs volumetric-modulated arc therapy associated with hippocampal sparing during prophylactic cranial irradiation. *Technol Cancer Res Treat* 20:15330338211043976. <https://doi.org/10.1177/15330338211043975>
- Yuen AHL, Wu PM, Li AKL et al (2020) Volumetric modulated arc therapy (VMAT) for hippocampal-avoidance whole brain radiation therapy: planning comparison with Dual-arc and Split-arc partial-field techniques. *Radiat Oncol* 15:42. <https://doi.org/10.1186/s13014-020-01488-5>

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