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Original Article

Oncology Section

Dosimetric Comparison of Hippocampal Sparing Whole Brain Radiotherapy by Volumetric Modulated Arc Therapy, Linac-based Intensity-modulated Radiation Therapy and 3-D Conformal Radiation Therapy: A Cross-sectional Study

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ABSTRACT

Introduction: Brain metastases are treated with Whole-Brain Radiotherapy (WBRT) using the 3-D Conformal Radiation Therapy (3DCRT) technique. Attempts have been made to perform dosimetric analysis of WBRT with hippocampal sparing using 3DCRT, Volumetric Modulated Arc Therapy (VMAT), and Linac-based Intensity Modulated Radiation Therapy (linac-based IMRT), anticipating technical challenges during contouring and treatment planning.

Aim: To perform a dosimetric analysis and comparison of hippocampal sparing cranial irradiation by 3DCRT, VMAT, and IMRT treatment plans in brain metastases patients.

Materials and Methods: The analytical cross-sectional dosimetric study was conducted from November 2022 to September 2023 at Government Medical College, Kottayam, Kerala, India. Ten patients treated for brain metastases with WBRT using 3DCRT were considered for dosimetric analysis. The Planning Target Volume (PTV) dosimetry and hippocampal dosimetry were studied for all ten patients. The important dosimetric parameters included volume receiving 100% dose, Target Coverage (TC), Homogeneity Index (HI) in PTV dosimetry, the mean hippocampal dose, and maximal hippocampal dose in hippocampal dosimetry. The hippocampus and hippocampal avoidance volume were contoured. Treatment plans for 3DCRT, VMAT, and Linac-based IMRT were generated for each patient's prescription dose of 30 Gy in 10 fractions. The non-parametric Kruskal-Wallis test was used for data analysis.

Results: The mean whole brain Planned Target Volume (PTV) was 1190 cm^3. The mean hippocampal avoidance volume was 30 cm^3, which occupied 2.5% of the whole brain PTV. The average median dose received by the hippocampus was 30.05 Gy, 17.1 Gy, and 17.5 Gy for 3DCRT, Linac-based IMRT, and VMAT, respectively. The mean dose for the hippocampus was 31.03 Gy, 17.7 Gy, and 17.5 Gy for 3DCRT, Linac-based IMRT, and VMAT, respectively ($p<0.001$). VMAT offered better hippocampal sparing compared to IMRT and 3DCRT. On average, VMAT offered a 2% improvement, and 3DCRT offered a 5% improvement in TC compared to IMRT. The HI of 3DCRT was 0.09, IMRT 0.199, and VMAT 0.150.

Conclusion: VMAT and LINAC-based IMRT permit hippocampal-sparing WBRT with adequate target volume coverage and acceptable homogeneity when compared to 3DCRT plans. Thus, the dosimetric study suggests that modern radiotherapy techniques should be advocated for hippocampal-sparing WBRT.

Keywords: Brain metastases, Hippocampal avoidance, Neurocognitive function

INTRODUCTION

Brain metastases, due to varying malignancies, are usually treated with WBRT. The hippocampus is a complex structure of the human brain associated with memory consolidation and decision-making. It is the grey matter tissue located in the Parahippocampal gyrus inside the inferior temporal horn of the lateral ventricle. The hippocampus, which is an integral part of the limbic system, has four parts: the hippocampus proper (Cornu Ammonis; CA), Dentate Gyrus (DG), subiculum, and Entorhinal Cortex (EC). Neuronal stem cells are located in two neurogenic niches: lining the walls of the lateral ventricle (subventricular zone, SVZ) and the dentate gyrus of the hippocampus (subgranular zone, SGZ). Neural stem cells play a pivotal role in hippocampal neurogenesis. The pyramidal and granule cells generated from mitotically active neural stem cells located in the subgranular zone of the dentate gyrus are associated with memory function. It regulates learning, memory encoding and consolidation and spatial navigation [1]. The stem cell niche of the hippocampus, responsible for neurocognitive function, is the most sensitive to the therapeutic doses of WBRT. They are rendered gliogenic, less proliferative and more apoptotic [2,3]. These effects are due to inflammation around the neural stem cells, as stated by Monje ML et al., [4]. During WBRT, inflammation of these "stem cell niche" and their damage imparts neurocognitive decline, notably in the memory-related domain [5,6].

Modern radiotherapy techniques like IMRT and VMAT ensure a conformal avoidance of the hippocampus and may spare patients from radiation-induced neurocognitive decline, without compromising on TC and homogeneity [7]. Newer radiation techniques like IMRT utilising Linac-based IMRT and VMAT can conformally spare the hippocampus during cranial radiation. This, in turn, reduces radiation-induced inflammation of the stem cell niche of the hippocampus, mitigating neurocognitive deficits [8]. Brain metastases, prophylactic cranial radiation for small cell lung cancer and paediatric malignancies are the common indications for WBRT [8]. Testing of hippocampal

sparing during WBRT in patients with brain metastases was initiated at the University of Wisconsin [9].

Mostly advanced malignancies of lung, breast, GIT can metastasise to the brain. Whole brain radiotherapy aimed at sterilising the brain metastases was commonly employed. With the advent of targeted and newer chemotherapeutic agents, these patients live longer than what was expected previously [10]. Herein, the authors did a dosimetric analysis and comparison of hippocampal sparing cranial irradiation treatment plans. Additional plans were generated for IMRT and VMAT techniques in brain metastases treated with WBRT by 3DCRT. The meaningful difference derived in hippocampal dosimetry by improved radiation techniques might lead to the stepping stone of hippocampal sparing WBRT in the study institution.

MATERIALS AND METHODS

The analytical cross-sectional study was conducted from November 2022 to September 2023 at Government Medical College, Kottayam, Kerala. Ten patients treated for brain metastases with WBRT using 3DCRT were considered for dosimetric analysis. Institutional ethical clearance with IRB No. 71/2022 was obtained.

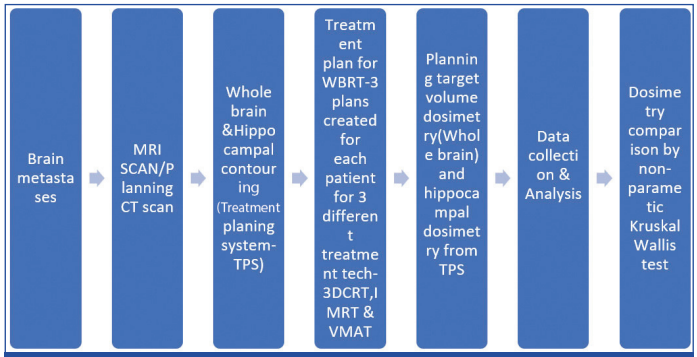
Inclusion criteria: Patients with brain metastases aged 20-70 years, ECOG performance status 0-3, and no previous history of radiation to the brain were included.

Exclusion criteria: Patients receiving WBRT by single radiation dose, metastases located in and around the hippocampus area, and those with a previous history of radiation to the brain were excluded.

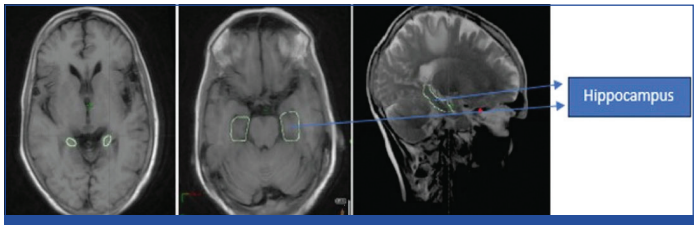
Ten patients being treated for brain metastases with WBRT using 3DCRT were considered for dosimetric analysis for the three techniques.

Procedure

Flowchart of methodology is shown in [Table/Fig-1]. Patients were immobilised with a thermoplastic head mask and underwent non-contrast CT simulation with 2 mm slices from the vertex to the chin. The CT axial images were imported and fused with axial T2-weighted and gadolinium contrast-enhanced T1-weighted sequence acquisitions Magnetic Resonance Imaging (MRI). The target (whole brain) and the avoidance region (hippocampus) were contoured [Table/Fig-2], and a treatment plan was generated with the Eclipse planning system (Varian Medical Systems, Palo Alto, CA, Version 16) for VMAT, IMRT, and 3DCRT techniques using 6MV photon beams. Thus, three treatment plans advocating the triple-A (AAA) algorithm were generated for each patient.

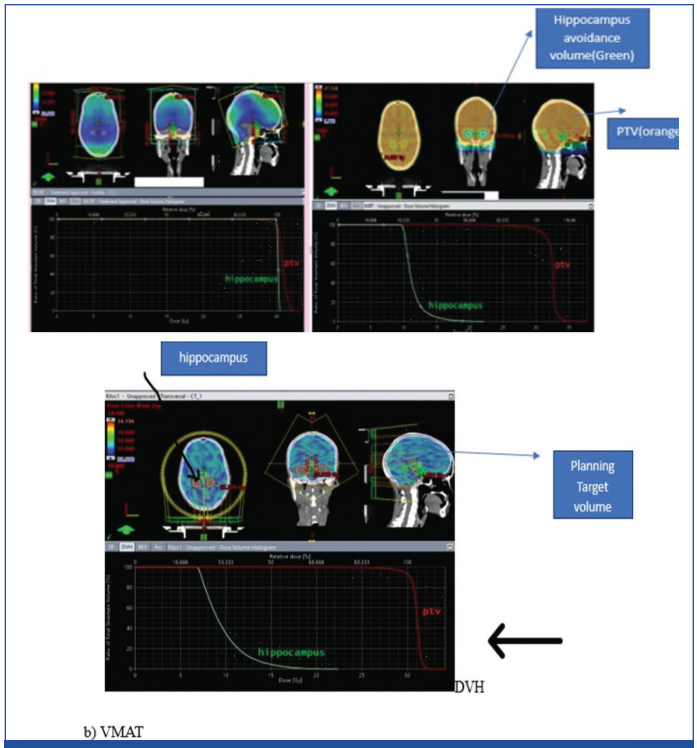


[Table/Fig-1]: Flow chart of methodology.



[Table/Fig-2]: Hippocampus contouring (green) on MRI fused images.

WBRT with 30 Gy in 10 fractions was delivered by 3DCRT. The dosimetric analysis and comparison of the three treatment plans were conducted, and the parameters were entered. [Table/Fig-3] shows a comparison of dose distribution and Dose-Volume Histogram (DVH) of HAWBRT (Hippocampal Avoidance WBRT) with: (a) 3DCRT; (b) VMAT; (c) IMRT.



[Table/Fig-3]: Comparison of Dose distribution and Dose-Volume Histogram (DVH) of Hippocampal-avoidance whole brain radiation therapy (HA-WBRT) with: (a) 3DCRT; (b) VMAT; (c) IMRT.

Compliance criteria for target and normal tissue planning doses (RTOG 0933):

- V30Gy >95% PTV (V30 Gy- Volume of whole brain PTV receiving 30 Gy)
- D2% PTV <37.5 Gy (D2%- Greatest dose delivered to 2% PTV)
- D98% PTV >25 Gy (D98%- Greatest dose delivered to 98% target volume)
- Hippocampus: Dmin=D 100%--<9 Gy (D100%-Greatest dose delivered to 100% bilateral hippocampi) Dmax=<16 Gy (Dmax-Dose to hottest 0.03 cc of bilateral hippocampi)

The T1 weighted MRI axial sequence was selected for hippocampal contouring. The gray matter was located inferomedial and fimbriae superomedial to the hippocampus. The hippocampus extends from the floor of the temporal horn and proceeds postero-cranially along the medial edge of the temporal horn to terminate at the lateral edges of quadrageminal cisterns. The PTV was the whole brain parenchyma, excluding the hippocampal avoidance region. The hippocampal avoidance region is created by adding a margin of 5 mm to the hippocampus.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 14.0 software. The comparison of the different PTV dosimetry and hippocampal dosimetry among three different techniques was done with the Kruskal-Wallis test (a non-parametric test of one-way ANOVA). Asymptotic significance (2-sided tests) displayed the level of significance at $p<0.05$.

RESULTS

The total of 10 included patients and tumour characteristics were enumerated in [Table/Fig-4].

Characteristics	Frequency (Total N=10 patients)	Percentage
Sex		
Male	1	10%
Female	9	90%
Primary tumour site		
1. Breast	6	60%
2. Lung	4	40%
Age	Median age 57 years	(Range 51-80)

[Table/Fig-4]: Patient and tumour characteristics.

The mean whole brain PTV was 1190 cm^3 (range 1040-1535 cm^3). The mean hippocampal avoidance volume was 30 cm^3 (range 21.2-41.6 cm^3), which occupied 2.5% (1.8-3.5%) of the whole brain PTV. The median dose received by the hippocampus was 30.05 Gy, 17.1 Gy, 17.5 Gy by 3DCRT, linac-based IMRT, and VMAT, respectively. On average, VMAT offers a 2% improvement and 3DCRT a 5% improvement in TC when compared to IMRT [Table/Fig-5]. The mean dose to 100% of the hippocampus was 30.05 (range 29.3-31.1) with 3DCRT, 9.5 Gy (range 8.5-14.9) with IMRT, and 7.8 Gy (range 6.7-12) for VMAT. The mean maximal hippocampal dose was 31.62 Gy (range30.5-32.4), 30.49 Gy (range 29.4-32), and 29.9 Gy (range 24.1-32.3) by 3DCRT, IMRT, and VMAT, respectively. The maximal dose here was more than what was suggested by RTOG, but the dose by VMAT and linac-based IMRT was significantly less when compared to 3DCRT (p=0.010) [Table/Fig-6].

Technique	Median dose-hippocampus	Improvement in Target Coverage (TC)
3 DCRT	30.05 Gy	5%
IMRT	17.1 Gy	1%
VMAT	17.5 Gy	2%

[Table/Fig-5]: Median hippocampal dose with improvement in Target Coverage (TC).

volume was 27.5 cm^3, which represented 2.1% of the whole brain [7]. Here, the mean whole brain PTV was 1190 cm^3 (range 1040-1535 cm^3). The mean hippocampal avoidance volume was 30 cm^3 (range 21.21-41.6 cm^3), which occupied 2.5% of the whole brain PTV.

In this study, VMAT offered better hippocampal sparing when compared to IMRT and 3DCRT. In the Wisconsin study of multi-institutional analysis [7], the median hippocampal dose was 5.5 Gy for IMRT and 7.8 Gy for helical Tomotherapy. Thus, helical Tomotherapy offered better hippocampal sparing than linac-based IMRT. The accepted alpha/beta ratio of the CNS is two [2], which is classified as a late responding tissue [12]. The pragmatic dose constraint to mitigate long-term neurocognitive decline is the mean dose of the left hippocampus of less than 30 Gy [13]. Besides, Jalali R et al., after their analysis of factors affecting neurocognitive decline stated that those patients receiving more than 42 Gy to the left hippocampus suffered greater than a 10% decline in their FSIQ (p=0.048) [14]. But RTOG 0933 protocol defined strict constraints to the target and Organ At Risk (OAR) [11]. According to the protocol, the dose to 100% of the hippocampus could not exceed 9 Gy, and the maximal hippocampal dose could not exceed 16 Gy. Dose to 100% of the hippocampus exceeding 10 Gy and maximal hippocampal dose exceeding 17 Gy cannot be accepted and require replanning [11].

TC denotes the fraction of the target volume (Vt) receiving at least the prescription dose (Vt pre.dose). For perfect coverage, TC equals one. In the present study, VMAT offers a 2% improvement, and 3DCRT offers a 5% improvement in TC when compared to IMRT. Helical tomotherapy demonstrated a 2% improvement in TC as stated by Gondi V et al., [7]. In this study, HI was best for 3DCRT followed by VMAT and then by IMRT. In the Gondi V et al., study, there was a rapid dose fall-off with helical tomotherapy, but homogeneity was acceptable with both IMRT modalities [7].

Result	PTV 3000CGy Dosimetry				Hippocampal dosimetry			
	D2% PTV	D50% PTV	D98% PTV	Volume receiving 100% dose (30 Gy)	Mean Hippocampal dose	Dose 100% hippocampi	Dose to 0.03 cc of B/L hippocampi	Treatment time
3DCRT	32.730	31.740	29.870	97.49%	15.545	30.05	31.620	11 min
IMRT	33.2010	30.960	26.960	91.96%	8.8615	9.5	30.490	14 min
VMAT	32.460	31.2970	27.750	93.8%	8.7	7.8	29.990	6 min
p-value	0.314	**<0.026**	**0.001**	**0.032**	**<0.001**	**<0.001**	**0.010**	

[Table/Fig-6]: Dosimetric comparison of various parameters by three different techniques and their p-value.
Bold p-values are significant

HI signifies the homogeneity of the dose within the target volume as specified by ICRU (International Commission on Radiation Units and Measurements). {HI=D2%-D98%/D median (D50%)} Smaller values for HI signify more homogeneous irradiation of the target volume. The HI of 3DCRT was 0.09, IMRT 0.199, and VMAT 0.150 (p=0.001) [Table/Fig-7].

Technique	Homogeneity Index (HI) $HI=\frac{D_{2\%}-D_{98\%}}{D_{median}}$ (Ideal-0)	Target Coverage (TC) $TC=\frac{V_{Tpresc}}{V_T}$ (Ideal=1)
3DCRT	0.090	0.974
IMRT	0.199	0.9196
VMAT	0.150	0.938
p-value	**0.001**	**0.001**

[Table/Fig-7]: Homogeneity Index (HI) and Target Coverage (TC) (comparison).
Bold p-values are significant

DISCUSSION

The dentate gyrus and conus ammonius targeted contouring enables avoidance of the subgranular stem cell compartment [11]. In the Gondi V et al., study, the mean hippocampal avoidance

Hippocampal sparing was achieved with acceptable TC and homogeneity for a prescription dose of 30 Gy in 10 fractions for brain metastases. VMAT and linac-based IMRT significantly reduced the dose to the hippocampus when compared to 3DCRT. The mean maximal dose here is greater than 16 Gy; hence, more meticulous planning and replanning to abide by this constraint would be required in the future. The apparent long-term neurocognitive benefit needs to be evaluated clinically. The study was a dosimetric analysis alone on additionally created VMAT and IMRT plans for each patient. The clinical significance can be ensured only after hippocampal avoidance treatment on patients undergoing WBRT with VMAT and IMRT.

Limitation(s)

The study is only a pilot study with a small number of patients. Here, a dosimetric analysis and comparison of PTV dosimetry and hippocampal dosimetry was done on computer-generated plans for 3D CRT, IMRT, and VMAT. The results may not be replicable or extrapolated unless tried on human subjects. The study only justifies the feasibility of IMRT and VMAT for HSWBRT. The functional benefit of the techniques on the neurocognitive domain could be assessed only after adaptation of these techniques for WBRT.

CONCLUSION(S)

Accurately delineating the hippocampus and identifying its central location are the two important challenges faced during contouring (RTOG 0933) and when attempting its sparing during IMRT and VMAT. However, by using these techniques for conformal avoidance, the authors could significantly reduce the mean dose received by the hippocampus compared to 3DCRT. Nevertheless, the postulate of mitigating neurocognitive decline needs to be evaluated by a clinical neurological examination, including Full Scale Intelligence Quotient (FSIQ), conducted by a multidisciplinary team of radiation oncologists, neuroradiologists, and neurologists.

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