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ORIGINAL ARTICLE

Comparison of Hippocampal Sparing Intensity Modulated Radiotherapy Plans in Patients of Brain Tumors treated by Three-dimensional Conformal Radiotherapy

Diksha Chaturvedi[1], Piyush Kumar[2], Arvind K. Chauhan[2], Pavan Kumar[3], Jitendra Nigam[4], Silambarasan N. Sivaji[4], Navitha Silambarasan[4]

ABSTRACT

Introduction: Radiotherapy plays a key role in brain tumors after surgery. However, concerns regarding neurocognitive toxicity after radiotherapy are being raised. Newer radiotherapy techniques can deliver radiotherapy with better precision planning and delivery. Effective hippocampal sparing is possible with IMRT which governs the neurocognitive functions. The present study is done to compare whether hippocampal sparing is possible in brain tumors by 3D Conformal Radiotherapy and Intensity Modulated Radiotherapy and their effects on neurocognitive functions.

Materials and Methods: Twenty-two patients with brain cancer were recruited from November 2019 to April 2021. Patients were treated with 3D-CRT technique and alternate IMRT plans were generated. Dosimetric parameters of PTV, organs at risk along with hippocampus were evaluated and compared for 3DCRT and IMRT plans. Neurocognitive functions were evaluated using MMSE score.

Result: In study group, there were 16 males and 6 females with median age 45 years. Brain tumors were commonly located in frontal lobe (36%) followed by parieto-occipital lobe (18%) and fronto-temporo-parietal lobe (13.63%). PTV parameters were better for IMRT and statistically significant. The OARs did not show significant difference except in both lens though they are within tolerance limits. There is no significant difference in the dosimetric parameters of hippocampus in 3D-CRT and IMRT plans. The p-value for Dmax is 0.79, Dmean is 0.26, Dmin is 0.18 between hippocampal sparing radiotherapy plans.

Conclusion: Anatomic location of tumor plays a key role in deciding hippocampal sparing. Patients whose NCFs showed improvement on subsequent visits, highlights the fact that primary tumor control is a key factor in deciding decline or improvement in NCFs. It should be beneficial for LGG that have better survival and prognosis as compared to HGG cases.

Keywords: Hippocampal sparing 3DCRT, IMRT, Neurocognitive function.

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[1]Junior Resident, [2]Professor, [3]Associate Professor, [4]Medical Physicist cum Assistant Professor

Department of Radiation Oncology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India

Corresponding Author: Dr. Piyush Kumar, Professor Department of Radiation Oncology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India, e-mail: piykumagr@gmail.com

INTRODUCTION

Radiotherapy is an important modality in the treatment of brain tumors. Radiotherapy remains the standard treatment for high-grade and low-grade gliomas after surgery. However, concerns regarding neurocognitive toxicity after radiotherapy in patients with benign or low-grade tumors make the timing of treatment controversial.[1]

Newer radiotherapy techniques have evolved for better precision planning and delivery. Studies conducted in the past were done over brain metastasis cases treated via whole brain radiotherapy (WBRT). The study was done to compare methods to reduce doses to hippocampus creating a hippocampal avoidance zone. Effective hippocampal sparing was made possible with the development of sophisticated radiotherapy delivering techniques such as intensity modulated radiotherapy (IMRT).[2-4]

Why is hippocampus so important as a structure is because studies have shown that hippocampus is one of the structures of the brain where neurogenesis continues even in adulthood.[5] Neurons generated here gets integrated into the mainstream neurons.

The hippocampus plays a key role in episodic memory, the capacity for the recollection of unique personal experiences and in particular aspects of the acquisition of semantic or factual knowledge. Papez *et al*[6] proposed that emotional response is organized in hippocampus and is expressed in cingulate gyrus via mammillary bodies. It has also been now implicated in recollecting the past experience and imagining future.[7]

While the tumor itself may affect the neurocognitive function (NCF) of patients, radiotherapy is also associated with declined NCF. The mechanism of radiation injury is complex and multi-factorial. In the past, cognitive decline

after radiotherapy was believed to be a late effect of treatment mediated through microvascular changes and neuroglial loss. However, there is increasing evidence for acute and subacute cognitive changes after radiotherapy that appear to be mediated through the neurogenic zones including the hippocampus.[8]

These studies have highlighted on the fact that even though plans were generated for sparing of hippocampus, it has not to compromise the tumor itself. However, unlike WBRT, the hippocampal-sparing strategy for the radiotherapy treatment of primary brain tumor has not been thoroughly evaluated. Although the dosimetric feasibility has been reported in a few studies.[2,9-11] Therefore, the present study was aimed to compare whether hippocampal sparing was possible in brain tumors by two different types of radiotherapy techniques - 3D Conformal Radiotherapy and Intensity Modulated Radiotherapy and whether there were any effects on neurocognitive functions by hippocampal sparing.

MATERIALS AND METHODS

The present study was conducted on 22 patients from November 2019 to April 2021 at Department of Radiation Oncology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.

Inclusive Criteria

Histologically proven brain tumor patients (low grade & high-grade glioma), age >18 years and karnofsky performance status >70 were included in study.

Exclusion Criteria

Patients with prior or synchronous malignancy, distant metastasis, previously treated patients of any brain pathology were excluded from the study.

Radiotherapy Planning

Simulation

All patients underwent thermoplastic cast preparation followed by Radiotherapy planning Computed Tomography of Head (CT-RTP) with 3mm slice thickness and magnetic resonance images (MRI) Brain with contrast for planning done in supine position with head first after consent. Tumor appearance on T1-weighted MRI is like that on CT, although tumor volumes are better delineated on MRI, particularly with low-grade neoplasms that do not demonstrate contrast enhancement. CT images then were fused with MRI Images. Treatment planning was optimized with MRI co-registration assisting delineating tumor, necrosis and edema with T1, T2 and fluid attenuation and inversion recovery (FLAIR) images.

Target Delineation

3D-CRT plans were generated using in Eclipse Treatment Planning System (TPS).

Low Grade Glioma: 54 Gy in 30 fractions at 1.8Gy/fraction, 5 days a week over 6 weeks.

- GTV: signal change on T2 MRI
- CTV: GTV + 1.5 cm

High Grade Glioma

Phase 1: 45 Gy in 25 fractions at 1.8Gy/fraction, 5 days a week over 5 weeks

- GTV1 = surgical resection cavity plus any residual enhancing tumor (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans).
- CTV1 = GTV1 plus a margin of 2 cm (if no surrounding oedema is present, the CTV is the contrast enhancing tumor plus 2.5 cm).

Phase 2: 14.4Gy in 8 fractions at 1.8Gy/fraction, 5 days a week over 1½ weeks

- GTV2 = surgical resection cavity plus any residual enhancing tumor (post contrast T1 weighted MRI scans)
- CTV2 = GTV 2 plus a margin of 2 cm

The planning target volume (PTV) was given a margin of 3 mm around CTVs, to account for patient setup error.

OARs Delineation

Delineation of organs at risk (OARs) was done including the brain, brainstem, spinal cord, optic chiasm, cochlea, optic nerves, eyes, lens and hippocampus. The delineation of the hippocampus on the MRIs was based on RTOG 0933 delineation protocol.[12] Expanded contours was created with safety margins of 3 mm around the brainstem & the chiasm and 5 mm around the optic nerve.

Hippocampus Contouring (According to RTOG 0933)

The hippocampus was contoured on T1-weighted MRI axial sequences. Given the preponderance of gray matter in the hippocampus, contouring focused on the T1- hypointense signal medial to the temporal horn and distinct from the T1-hyperintense parahippocampal gyrus and fimbriae, located inferomedial and superomedial to the hippocampus, respectively. Contouring was initiated at the most caudal extent of the crescentic shaped floor of the temporal horn and continued postero-cranially along the medial edge of the temporal horn. The medial border of the hippocampus was delineated by the edge of the T1-hypointensity up to the ambient cistern. The uncal recess of the temporal horn served to distinguish the hippocampus from the gray matter of the amygdala, lying anterior and superior to the hippocampus. The postero-cranial extent of the hippocampus was defined

by the curvilinear T1-hypointense hippocampal tail located just antero-medially to the atrium of the lateral ventricle. Contours will terminate at the lateral edges of the quadrageminal cisterns, prior to the emergence of the crus of the fornix. Appropriate anatomical contouring was confirmed using T1-weighted MRI sagittal and coronal sequences. No hippocampal avoidance zone was created for these patients.

Radiotherapy Planning Techniques

3D CRT Technique: Using CT scanning and MLCs, volumes were tailored to avoid as much normal tissue as possible. Three beam arrangements were often be used, which may be noncoplanar and may be wedged as appropriate to obtain a satisfactory dose distribution. *IMRT Planning:* Coplanar multiple fields around isocenter using isotropic gantry angles were used and may be adjusted slightly to avoid the beam entry through OAR's. In next step of fluence Optimization, the dose coverage minimum and maximum required for PTV and dose tolerance to OAR's are defined. Optimize fluence were calculated for LINAC specification. Now the plan was evaluated by two methods isodose coverage and DVH. Plan may be compared with alternate plan, to improve treatment quality.

To normalize the plan the planning goal will have a homogeneity between -5% and +7% (95% to 107%). All patients were treated using 3DCRT technique.

Simultaneously IMRT plans were generated to compare the dosimetric parameters (not planned for treatment purposes).

Dosimetric Assessment

- Dose–volume histograms (DVHs) corresponding to the delivered 3-D CRT and then comparison with IMRT plan was done for each contoured region.
- All planning techniques were evaluated using dose-volume histogram (DVH). PTV dosimetric parameters for evaluation were as follows: PTV receiving 95% dose is designated as PTV (V95%), dose given to 95% PTV is designated as PTV (D95), maximum dose to the PTV (D_{max}), mean dose to the PTV (D_{mean}), conformity index (CI) and homogeneity index (HI). The CI is defined as, CI = TV/PTV where TV was the volume of treated reference dose (95%) of PTV prescription. CI value closer to 1 indicates a conformal plan. The HI is defined as HI=(D2%-D98%)/D50%, where D2%,98% and 50% of the PTV volume. HI value closer to 0 indicates a homogeneous plan. The volume of other OARs receiving dose were quantified and these dosimetric parameters are designated as follows:

* PRV Brainstem: D_{max}, PRV Spine: D_{max}, PRV Optic chiasma: D_{max}, Optic nerve (Right & Left): D_{max}, Cochlea bone (Right & Left): D_{mean}, Eye (Right & Left): D_{max}, Lens (Right & Left): D_{max}

* Hippocampus: Dmax, Dmean and V20

Both the plans (3D-CRT and IMRT) were evaluated on the basis of above mentioned PTV and OAR parameters.

Neurocognitive Function Tests

Neurocognitive function tests were performed using Mini Mental State Examination (MMSE). A MMSE score between 24-30 is no cognitive impairment (N), 18-23 shows mild cognitive impairment, 0-17 depicts severe cognitive impairment. They were done before starting of treatment (0 months), at 3 months & 6 months post completion of treatment.

Follow Up

Patients were assessed weekly during Radiotherapy, at the end of Radiotherapy and thereafter monthly upto 6 months. Neurocognitive function tests were done with multiple questionnaire at start of treatment, at 3 months & 6 months post completion of treatment.

Statistical Analysis

Collected data are analyzed using standard statistical methods and software (t-test two sample of unequal variances; Annova – three factors test to calculate level of significance using "p" value. "p" value of less than 0.05 is taken as significant in our study.

RESULTS

Twenty two patients with gliomas were recruited from November 2019 to April 2021. Patients were treated with 3D-CRT technique. Alternate plans were generated for the same patients using IMRT technique to evaluate the dosimetric parameters, in terms of PTV and organs at risk including hippocampus.

In study group, out of 22 brain tumors cases, 16 male and 6 females were found. The mean age was 44.40 years, median age was 45 years and age range were 22–62 years.

Brain tumors are more commonly located in frontal lobe (36%) followed by parieto-occipital lobe (18%) and further followed by fronto-temporo-parietal lobe (13.63%). In this study, it was found that high grade glioma (HGG) is the most common grade and approximately 54% patients belonged to high grade glioma group and approximately 45% belonged to low grade glioma (LGG). In the study it was found that majority of the patients had atleast one episode of seizure along with memory changes, mood changes, headache being most common symptom.

Comparison of planning target volume (PTV)between 3DCRT and IMRT is shown. PTV parameters were better for IMRT statistically significant. (Table 1)

Comparison of dosimetric parameters of OARs in 3DCRT and IMRT is shown. These parameters does not show significant difference except in both lens though they are within tolerance limits (Table 2).

There is no significant difference in the dosimetric parameters of hippocampus in 3D-CRT and IMRT plans. The p-value for Dmax is 0.79, Dmean is 0.26, Dmin is 0.18 between hippocampal sparing radiotherapy plans (Table 3).

Neurocognitive function evaluation by MMSE at 0-, 3- and 6-months results were interpreted as - a score between 24-30 is no cognitive impairment (N), 18-23 shows mild cognitive impairment and 0-17 depicts severe cognitive impairment. The mean value of MMSE at 0 months is **18.82**, at 3 months is **18.90**, at 6 months **18.63.** There is MILD cognitive deficit noted**.** The *p*-value is not significant (0. 89) (Table 4).

Table 1: Comparison of dosimetric parameters PTVbetween 3DCRT and IMRT

	3DCRT	*IMRT*	*p-value*
V95%	92.89+/-2.64	98.644+/-1.57	0.002
D95 (Gy)	53.498+/-2.71	56.111+/-2.93	0.003
D_{max}	61.916+/-2.92	59.897+/-0.50	0.08
D_{mean}	57.708+/-2.63	55.851+/-9.11	0.36
CI	1.47+/-0.25	1.247+/-0.15	0.001
HI	0.210+/- 0.15	0.075+/-0.065	0.009

Table 2: Comparison of dosimetric parameters OARs in 3DCRT and IMRT

OARs		*3DCRT*	*IMRT*	*p-value*
Brainstem (D_{max})		51.4	48.5	0.23
PRV Spine (D_{max})		14.5	8.9	0.11
Optic chiasma (D_{max})		47.2	43.4	0.29
Optic nerve	Right	35.9	32.4	0.60
(D_{max})	Left	35.2	28.5	0.22
Cochlea	Right	20.8	18.7	0.74
(D_{mean})	Left	20.9	17.8	0.61
Eye	Right	16.2	23.2	0.11
(D_{max})	Left	20.9	22.2	0.09
Lens	Right	3.1	5.4	0.01
(D_{max})	Left	3.4	5.4	0.06

Table 3: Comparison of dosimetric parameters between 3DCRT v/s IMRT

SERIAL NO.	3D-CRT			IMRT		
	Dmax	Dmean	Dmin	Dmax	Dmean	Dmin
1	36.3	24.3	17.2	23.0	13.1	6.07
2	59.9	52.6	22.5	60.9	46.5	16.4
3	59.3	41.8	16.1	60.3	38.9	18.6
4	59.8	40.5	18.2	59.2	41.6	19.4
5	44.5	17.9	4.2	15.4	8.9	3.6
6	50.6	37.1	2.5	52.3	31.6	17.9
7	41.9	13.8	2.2	12.5	4.2	1.72
8	51.0	48.6	44.5	54.1	42.9	30.1
9	53.7	39.0	22.4	54.9	38.3	18.0
10	55.1	53.2	52.2	55.3	52.6	39.4
11	53.6	37.0	13.3	55.8	28.9	17.3
12	54.1	36.2	4.5	55.0	35.3	16.0
13	44.7	39.7	16.5	49.5	27.9	16.9
14	59.8	42.6	35.5	61.1	36.1	20.8
15	46.2	44.9	44.4	52.9	45.6	33.8
16	49.2	34.6	16.4	54.1	23.9	3.2
17	45.6	9.1	2.4	56.8	32.5	17.8
18	59.8	54.0	44.2	60.5	43.7	20.8
19	58.4	45.9	37.8	63.1	40.8	17.2
20	58.7	47.1	38.2	62.1	43.3	20.2
21	53.1	47.0	38.8	56.4	35.9	13.3
22	56.2	46.4	31.1	56.4	46.9	35.8

DISCUSSION

Radiation therapy (RT) has got its important role for treatment in primary brain tumors, providing local control or prolonged progression-free survival in most patients with primary brain tumors. On the other hand RT gives a negative impact on cognitive functioning which deteriorates quality of life. Cognitive dysfunction is defined as impairment in one or more cognitive functions which encompasses attention, memory, language, and executive function. The reason behind this cognitive dysfunction in brain tumor patients is multifactorial, which can be by the tumor itself, tumor-related epilepsy and treatment related factors such as neurosurgery, RT and chemotherapy. At present limited data is available for cognitive loss in brain tumor cases with reported prevalence ranging from 19% to 83%.[13] The hippocampus has been a major target in memory research since the seminal work of Scoville and Milner (1957). Human and animal lesion studies have shown that the hippocampus and other medial temporal lobe structures are involved in atleast some aspects of declarative memory. In our study of hippocampal sparing radiotherapy plans, we aim to study whether we can spare any doses to hippocampus without compromising target volumes.

Age

The study by Posti *et al.*[14] reported main presenting symptoms as seizures and cognitive disorder. Cognitive

Table 4: Neurocognitive function evaluation by MMSE (0, 3, 6 Months)

SERIAL NO.	MMSE					
	0 MONTHS		3 MONTHS		6 MONTHS	
	SCORE	CATEGORY	SCORE	CATEGORY	SCORE	CATEGORY
1	23	MILD	23	MILD	22	MILD
2	23	MILD	23	MILD	23	MILD
3	6	SEVERE	6	SEVERE	6	SEVERE
4	3	SEVERE	3	SEVERE	5	SEVERE
5	26	N	28	N	29	N
6	30	N	30	N	30	N
7	9	SEVERE	10	SEVERE	10	SEVERE
8	29	N	29	N	28	N
9	29	N	29	N	29	N
10	7	SEVERE	7	SEVERE	7	SEVERE
11	23	MILD	23	MILD	24	N
12	30	N	28	N	28	N
13	26	N	26	N	26	N
14	6	SEVERE	6	SEVERE	2	SEVERE
15	26	N	28	N	28	N
16	24	N	24	N	26	N
17	10	SEVERE	7	SEVERE	7	SEVERE
18	10	SEVERE	10	SEVERE	10	SEVERE
19	20	MILD	29	N	29	N
20	11	SEVERE	4	SEVERE	12	SEVERE
21	21	MILD	23	MILD	23	MILD
22	22	MILD	20	MILD	20	MILD

disorder is most often seen in age group above 51 years. Canyilmaz *et al.*[15] study had patients with median age 53 years and age ranged from 31–75 years whereas study by Hofmaier *et al.*,[16] median age was found to be 65 years age range of 28–82 years. The study by Kim *et al.*,[17] the median age was 49.5 years (26–77). Bioscience report by Tian *et al.*[18] included SEER databasewhich had patients ranging from < 40 to >60 age group.In our study, the mean age was found to be 44.40 years, median age was 45 years and age range was 22-62 years.It can be concluded that due to advancing technologies and increased awareness and alertness among population,diagnosis at earlier age is seen.

Sex

Canyilmaz *et al*[15] study with 20 patients where 13 (65%) males and 07 (35%) females, Hofmaier *et al*[16] 17 (63%) were males and 10 (37%) were females. Kim *et al.*[17]study, 11 (42.3%) males and 15 (57.7%) female patients were found to have primary brain tumor. Although Kim *et al.*[17] study showed increased female cases, studies have shown that gender plays a prognostic role in survival of GBM cases due to estrogen hormone acting as a protective function though no clear-cut evidence could be collected, reseach work is ongoing to find out its importance but as far as our study is concerned, we found similar result as Canyilmaz *et al.*[15] and Hofmaier *et al.*[16] study.

Symptoms

Posti *et al.*[14] concluded in his study that the main presenting symptoms of glioma in adults (MRI era) were seizures and cognitive disorder. A symptom prevalence based systematic review by Korevaar *et al.*,[19] found that seizures (37%), cognitive deficits (36%), drowsiness (35%), dysphagia (30%), headache (27%), confusion (27%), aphasia (24%), motor deficits (21%), fatigue (20%) and dyspnoea (20%). Seizures showing greater prevalence in all grades of tumor. In our study it was found that patients had headache (63%) as a common presenting complaint and atleast one episode of seizure (36%), 6 (27%) patients reported of visual disturbances, six patients with memory alteration (27%).

Tumor Site

Larjavaara *et al*[20] study gliomas were in 40% frontal lobe, 29% temporal, 14% parietal, 3% occipital lobe, and 14% in the deeper structures. The area with more frequent involvement of the right hemisphere (51%) than the left (40%). Eleven gliomas were noted in the center of the brain. The study was conducted showed the frequency to be highest for the frontal lobe, followed next by the temporal, parietal, and lastly the occipital lobe with a p-value to be 0.001. Canyilmaz *et al.*[16] study showed the most frequent lobe involved was parietal and temporal lobes in first position followed by temporo-parietal and temporo-occipital at second place and lastly fronto-temporal and frontal lobe.

In our study, the result was in accordance with Larjavaara *et al.*[20] study. The most commonly site involved was located in frontal lobe (36%) but instead of temporal or parietal lobe being next in frequency it was parieto-occipital lobe (18%) followed by fronto-temporo-parietal lobe with involvement of left which is in accordance with cerebral hemisphere (55%) with right cerebral hemisphere involvement seen in 40% of cases.5% of cases being bilateral/central presentation as per Larjavaara *et al.*[20] Temporal lobe involvement in 36% of cases.

PTV / Hippocampal Dose Parameters

There are several considerations when applying the hippocampal-sparing strategy to primary brain tumors. First, compromising the target volume for hippocampal sparing is not recommended. The American Society for Radiation Oncology (ASTRO) guidelines[21] for glioblastoma got to highlight that given the absence of published data for the hippocampal-sparing in glioblastoma patients, the panel is not recommending compromising the target coverage for hippocampus protection.

A study by Sood S *et al.*[22] compared VMAT to IMRT. There was lower hippocampus mean and maximum doses in VMAT than IMRT. The maximum hippocampus dose ranged between 15·5 and 19·2 Gy and between 18·4 and 20·6 Gy in VMAT and IMRT, respectively. The mean dose of the hippocampus ranged between 11·5 and 17·7 Gy (VMAT) and between 13·2 and 18·3 Gy (IMRT) concluding that using WBRT-SIB technique, VMAT showed better PTV coverage with less mean and maximum doses.

In our study, though PTV parameters were significantly better in IMRT plans than 3DCRT, no target volume (PTV) was compromised to spare hippocampus. The three patients in whom hippocampal sparing was possible did not compromise on target volume since the tumor location was far from PTV. The hippocampal doses were high D_{max} ranging from 12.5 to 63.1Gy and D_{mean} ranged from 4.2 to 52.6 Gy due to overlapping of PTV and hippocampal region.

In a dosimetric study presented by Lee *et al.*,[23] three patients were evaluated using VMAT and IMRT approaches in whole brain (WB) irradiation. Both techniques achieved satisfactory hippocampal sparing; however, VMAT was associated with a more homogenous PTV distribution.[24] In our study the patient population was gliomas who were planned radical doses and not WBRT. Hippocampal sparing was not possible due to increased dose prescription and location of tumor.

Hofmaier *et al.*,[16] compared 3DCRT versus VMAT plans in GBM patients, with a dose prescription of 60Gy in fractions of 2 Gy was planned. Hippocampal dose and treatment parameters were compared to the 3D-CRT plans. The influence of tumor location and PTV size on the hippocampal dose was investigated. Results showed that the median reduction of the contralateral hippocampus generalized equivalent uniform dose (gEUD) with VMAT (36%) compared to the original 3D-CRT plans ($p < 0.05$). The study also highlights on the fact that the more parietal the tumor the less chances of sparing hippocampus and the more temporal lower doses were received by contralateral hippocampus. In their conclusion they added that for larger PTV sizes, less sparing can be achieved.

In our study, both low grade glioma (LGG) and high grade glioma (HGG) were included. The dose prescription was less in LGG (54 Gy in 30 ractions) in comparison to HGG (59.4 Gy in 33 fractions).The hippocampus sparing could not be achieved with either of the dose prescriptions due to the tumor location in the vicinity of hippocampus, as also suggested by Hofmaier *et al.*[16]

Further in our study in around 31% of patients, the parietal lobe was involved, and we could not spare the hippocampus in any of these patients. Hofmaier *et al.*[16] also highlights the same fact.

Following the RTOG guidelines for delineation of LGGs and HGGs, the PTV volumes were too high in majority of the cases which again was a crucial factor that the sparing of the hippocampus in such cases was not possible. Similar findings were also noted by Hofmaier *et al.*[16] Sparing of hippocampus by compromising PTV will not be a good decision which has also been suggested in ASTRO guidelines.

Hippocampus being a bilateral structure, cases where the ipsilateral hippocampus is close to the target volume, sparing of the contralateral (C/L) hippocampus is suggested using the IMRT technique. Hofmaier *et al.*[16] comments on the dosimetry of contralateral hippocampus which gives a suggestion of evaluating the hippocampus in two parts (ipsilateral I/L) and C/L). The hippocampus is a continuous structure where QUANTEC guidelines mentions the dose constraints of D_{max} less than 16 Gy. Evaluating hippocampus on two sides (I/L and C/L) may not be so useful considering these facts but further studies may help to know the importance of laterality evaluation of dosimetry of hippocampus.

A retrospective study by Sood *et al.*[22] on 10 patients investigated the feasibility of WBRT using VMAT to spare the hippocampi and other above-mentioned OARs. Volumetric modulated arc therapy reduced cochlea mean and maximum dose by an average of 4 Gy (13%) and 2 Gy (6%), respectively. They concluded that the feasibility of WBRT using VMAT to not only spare the hippocampi, but also significantly reduce dose to OARs. In our study, D_{mean} for Right and Left cochlea was similar 20.8 Gy in 3DCRT plans and in IMRT plans 18.6Gy and 17.8Gy respectively. Though there was no significant difference between D_{mean} of cochlea in 3DCRT and IMRT plans, but all patients could achieve a dose constrain t of D_{max}<45 Gy, as per RTOG guidelines.

Awad *et al.*[25] analysed the VMAT approach in hippocampus sparing in 35 patients treated with WBRT, SIB or both. In 23 patients, the median dose for WBRT was 30Gy, while the median dose to brain metastases was 50 Gy (range: 20–70·8 Gy) delivered in a median of 15 fractions. The mean dose of the hippocampus ranged from 4·3 to 18.0Gy and the maximum dose ranged from 8·4 to 32·2 Gy. The wide range of mean hippocampus dose is related to the wide range of dose prescription, giving a priority to the target coverage by omitting hippocampus avoidance if the target is within 10mm close to the hippocampus. In our study, the dose prescription ranged from 54 Gy to 59.4 Gy in patients of LGG and HGG. As suggested by Awad *et al.*,[25] priority was given to the PTV and hippocampal sparing was avoided, so was the decision taken in all our cases. This is the reason the D_{max} in 3DCRT and IMRT were 52.3 and 51.4 Gy respectively and D_{mean} was 38.3 and 34.5 Gy, respectively. Only three cases could achieve the hippocampus D_{max}< 16 Gy as per RTOG guidelines because the tumor location in these 3 cases was not in close vicinity to the PTV.

The study by Marsh *et al.*[26] which included 12 patients of which 5 were of high grade glioma 5 with low grade glioma and 2 patients with brainstem low grade glioma it was brought to light that for centrally located primary brain tumor, hippocampal sparing radiation was not possible especially in those cases where tumor was adjacent to it or reaching to it. In our study, there was only one patient (5%) which was centrally located, and we could not spare the hippocampus. The patient received a D_{max} of 44.4 Gy to hippocampus. On retrospective IMRT plan the D_{max} was 49.6 Gy, concluding that it is difficult to spare hippocampus where tumor in located in central region.

In dosimetric studies of high grade gliomas, when IMRT is compared with three-dimensional conformal irradiation, IMRT is superior in limiting exposure for organs at risk (OAR) and allows for the planned target volume coverage.[27,28] However to spare the hippocampus the location of tumor and the size of PTV are an important factors. The PTV volumes are smaller for LGGs in comparison to HGGs. The dose prescription is also less than HGG. Therefore, LG tumors may have more chances of sparing hippocampus if the tumor is placed at an optimum distance from hippocampal region. Moreover,

hippocampal sparing in LGGs becomes more important due to their increased survivals so that long term NCFs could be prevented.

Neurocognitive Function

WBRT using 3D conformal radiotherapy is used as the standard technique in patients with multiple brain metastases. Many studies have confirmed that the function of hippocampus is affected by radiotherapy and consequently raising the risk of decline in NCFs.[29,30] In WBRT, less dose is planned for whole of brain to be treated whereas in glioma cases dose upto 60 Gy is planned. Therefore hippocampal sparing is more feasible in WBRT.

Murray *et al*.[31] showed the importance of MMSE in predicting outcomes in patients of brain metastasis where accelerated fractionation of 30Gy in 10 daily fractions of 2 Gy per fraction in 2 weeks was delivered. The average MMSE was 26.5 (range 11–30). In the follow-up, 62 patients died before obtaining follow up MMSE and 30 patients had a baseline of 30 and therefore no improvement could be expected. Of remaining 88, 54.5% demonstrated improvement in MMSE in follow up visits. Lack of decline of MMSE was seen in long term survivors. In our study of LGGs and HGGs the average MMSE score at 0 months, 03 months, and 06 months is almost 18.8, 18.9, 18.6 respectively. The range of MMSE score is almost similar at 0,03 and 06 months which is 03-30, 03-30, 2-30, respectively. In our study 8 patients (36.3%) had no cognitive dysfunction (MMSE 24-30) before start of the treatment and no deterioration was seen in NCFs in follow-up of 6 months.

The three patients where the hippocampal sparing was seen had MMSE score of 9 (severe impairment), 23 (mild) and 26 (no cognitive defect). In the follow up of these patients for 06 months, the MMSE score was 22 (mild), 29 (no cognitive defect), 10 (severe) thereby indicating no change in status of NCFs. Any improvement of NCFs in these patients will be dependent upon the disease status and a long term follow-up.

Two patients who showed improvement in NCFs, where hippocampal sparing was not achieved, the first patient with MMSE score 23 (mild) improved to MMSE score of 24 (no cognitive dysfunction) and the second patient improved the MMSE score from 20 (mild) to a MMSE score 29 (no cognitive dysfunction).The possible reason for improvement of NCFs in these patients may be due to improvement in disease status. Longer follow-up will be needed to really ascertain the improvement of NCFs in these two patients where no hippocampal sparing was seen.

Brown *et al*.[32] included patients with LGGs to undergo baseline MMSE. MMSE scoring of ≤26 had a worse 5-year progression-free survival rate (27% vs. 60%; $p < 0.001$) and overall survival rate (31% vs. 76%; $p < 0.001$) compared with those with a normal score. In our study, there were 9 patients (45.4%) of LGGs where 5 patients (55%) had MMSE score less than 26. Long-term follow-up of all these patients will be needed to validate whether the MMSE score is related to progression free survival (PFS) and overall survival (OS).

In study by Aoyama *et al*.[33] the NCF by MMSE was evaluated in the patients treated with WBRT plus stereotactic radiosurgery (SRS) and stereotactic radiosurgery alone. They observed that in a group of 92 patients who underwent follow-up MMSE, 39 had baseline MMSE less than equal to 27 (17 in the WBRT+SRS group and 22 in the SRS-alone group). Improvements of less than equal to 3 points in the MMSEs of 9 WBRT+SRS patients and 11 SRS-alone patients ($p = 0.85$) were observed. They concluded that the control of brain tumor is the most important factor for stabilizing NCF. In our present study eight patients had a baseline MMSE score of 24 and above suggesting no neurocognitive dysfunction. In a follow-up of six months, seven patients showed no change in MMSE score, eight patients showed improvement in MMSE score (range 1-9) and six patients showed deterioration of MMSE score (range 1-4). Only one patient had a notable change in MMSE score (from 20 to 29) though Hippocampal sparing was not seen in this. This can be attributed to the improvement of disease status after radiotherapy. Slight improvement or deterioration in MMSE scoring, may or may not be related to change in clinical outcomes in terms of NCFs. The absolute score of MMSE correlating with the change in NCF needs a longer follow up on these patients. As stated by Aoyama *et al*.,[33] the control of brain tumor is most important predictor of stabilizing NCF which means the improvement in disease status as well as increase in survivals in such patients is very important to assess the NCFs as well as the role of MMSE.

The mean value of MMSE score in our study was found to be at 0 months was **18.82**, at 3 months was **18.90**, and at 6 months was **18.63** which falls under moderate category.

MMSE scores [34] showed though not significant results in our study results were promising.Three patients whose hippocampal dose was found to be less in IMRT planning (not intended for treatment purpose here), MMSE showed no change in their category when treated via 3DCRT planning. It could be possible that if treated via IMRT planning these patients may show improvement in their scoring.

In study by Kesteren *et al*.,[35] where different arc radiotherapies were planned for sparing hippocampus use ofof non-coplanar beams arrangement, where it

was observed even higher hippocampal preservation compared to classical coplanar irradiation. One can plan for studies using different beam arrangements for sparing of hippocampus. As these plannings require higher expertise added to it are time consuming, in increased load of radiotherapy planning it will become a tedious task practically, but one may use these in further studies to see the possibility of hippocampal sparing.

Further VMAT, a newer form of radiotherapy planning may help in better hippocampal sparing. Different planning modalities used for hippocampal sparing needs a validation in terms of preservation of NCFs in long term follow up.

CONCLUSION

The present study found that PTV plays an important role interpret whether hippocampus could be spared or not. PTV cannot be compromised to spare hippocampus. Anatomic location of tumor plays a key role in deciding hippocampal sparing. Further, patients whose NCFs showed improvement on subsequent visits, highlights the fact that primary tumor control is a crucial factor in deciding decline or improvement in NCFs. Longer follow-up of these patients is needed to see their NCFs. This will especially be beneficial in LGG cases that have better survival and prognosis as compared to HGG cases.

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