ISSN 2515-8260 Volume 9, Issue 4, Winter 2022

Hippocampal sparing in radiation therapy to primary brain tumors - and impact on memory function in adults

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Abstract

Introduction - Sparing the hippocampus during cranial irradiation poses important technical challenges with respect to contouring and treatment planning.Purpose of this study was to assess if sparing the hippocampaus region during the planning of radiotherapy using IMRT technique without compromising the dose conformity to tumour, and to compare memory function of patient, before the start of irradiation and retention after radiation therapy in both the arms using the Hopkins verbal learning test.

Materials and Methods -Patients presenting with Primary brain tumours were chosen for the study. Age 18 to 65 years, diagnosis as per WHO Grading, ECOG performance status {0-2} were selected. All the types of Primary brain tumours were included.

Results - Uniform age distribution was noted among patients in both the arms .With 79.41% of the patients in the age group of 21-60years.Central nervous system tumours have a male predominance and the same was observed in our study with a total of 23 patients out of 34 being male (67.64%).About 88.23% of the patients in the 3D-CRT and 58.82% in the IMRT group did not show any neurological deficits. 1 patient each showed involuntary movement and hemiparesis type of neurological deficit in the 3D-CRT & the IMRT group. Loss of vision was noted in 1 patient. WHO Grading of the tumor at the stage of diagnosis not only provided us with a universal diagnosis but also helped in deciding the dose of radiation to be delivered as well as planning and providing the accurate treatment. The mean Hopkins score at 6 months interval in the 3D-CRT & IMRT group was found to be 10.18 ± 1.01and 10.82 ± 0.95, which was found to be statistically significant with a p value of 0.032.It was hypothesized that minimizing radiation dose to the least possible level in hippocampal region might delay or reduce the onset, and/or

severity of neurocognitive deficit.

Keywords - Hippocampalsparing, radiationtherapy, Primary brain tumours

Introduction

Primary intracranial tumors are of ectodermal and mesodermal origin and arise from the brain, cranial nerves, meninges, and pituitary, pineal and vascular elements. The majority of CNS tumors in adults arise in the supratentorial compartment. Most arise in the parenchyma and the majority of these are high-grade gliomas. Gliomas are the most common primary brain tumors and arise from astrocytes (Astrocytoma's), oligodendrocytes (Oligodendrogliomas) or ependymal cells (Ependymomas). SEER data estimated new cases of Brain tumours in 2021 is 24,530 which constitutes 1.3 % of all new cancer cases[1].

Brain and CNS (both malignant and non-malignant) tumors have an average annual age-adjusted incidence of 28.57 per 100,000 population. The incidence is higher in men (male to female ratio is approximately 1.6:1.1. Consolidated report of Hospital based cancer registries (2012-2016) by NCRP 2020 (survey conducted by Indian Council for Medical Research) on incidence of tumors of Brain & nervous system in India revealed; 3.4% in Delhi ,2.8 % in Mumbai, 3.8 % in Bangalore, 0.9% in Chennai among the males. In females 2.2% in Delhi, 2 % in Mumbai, 1.9% in Bangalore, 0.6% in Chennai. Gliomagenesis is the malignant transformation of normal glial cells (astrocytes or oligodendroglia cells)[2].

In 60% of low-grade gliomas P53 is rendered inactive by gene mutation or gene deletion. The progression into anaplastic astrocytoma and glioblastomamultiforme (40% of GBM are secondary GBM) is accompanied by RB and PTEN mutations with cell aneuploidy and overexpression of cyclin-dependent kinase 4 (CDK4) [3]. Primary GBM often (60%) show amplification of the epidermal growth factor receptor (EGFR), deletions in the INK4a gene with loss of p14 and p16 and diploid cells & PTEN mutation.3 The imaging modality of choice for CNS tumours is MRI, which demonstrates neuroanatomical and local pathological features in exquisite detail. Computed tomography (CT) scans are primarily used as an infrastructure for radiation treatment planning prior to fusion with MRI images [4].

External beam irradiation (EBRT) has historically been the cornerstone of the therapeutic approach to Gliomas. Conventional external-beam radiotherapy commonly is started 2 to 4 weeks after surgery to allow wound healing. Typically, a dose of 54 to 60 Gy is delivered in 1.8-

2 Gy per fraction over a period of 5 to 6 weeks.

MRI-based planning with Three-dimensional conformal therapy (3DCRT) is increasingly used in the treatment of primary brain tumours. The use of intensity- modulated radiotherapy (IMRT) yields conformal dose distributions and better avoidance of organs at risk.5 Hippocampus belonging tpthe limbic system plays important roles in the consolidation of information from short-term memory to long- term memory and spatial navigation [5].

Memory impairment is a well-documented side effect of cranial irradiation, but the underlying cause is ill-defined. One possible hypothesis focuses on a neurogenic stem cell compartment in the hippocampus that is highly sensitive to radiation and potentially central to radiation induced memory impairment. Various interventions and techniques have been tried to help in preventing neurocognitive decline due to cranial irradiation, one of the commonly used technique is Hippocampal-sparing [6].

Purpose of this study was to assess if sparing the hippocampaus region during the planning of radiotherapy using IMRT technique without compromising the dose conformity to tumour, and to compare memory function of patient, before the start of irradiation and retention after radiation therapy in both the arms using the Hopkins verbal learning test [7].

Materials and Methods

Source of data

Patients presenting with Primary brain tumours.

Inclusion criteria

Age 18 to 65 years, diagnosis as per WHO Grading, ECOG performance status {0-2}. All the types of Primary brain tumours.

Ethical considerations

After obtaining approval and clearance from the institutional ethics committee, 34 patients who have undergone surgical resection and who fulfilled the inclusion criteria were enrolled for the study. They underwent all the preliminary investigations. Informed consent and initial memory assessment of the patient using the HVLT- questionnaire was obtained from the Patient2 weeks

before proceeding with the treatment [8].

Analysis performed

Patients were selected and assigned randomly (17 cases each) among the the two arms

ARM A: Patients with primary brain tumors and treated with Hippocampal Sparing Radiation Therapy Using IMRT techniques.

ARM B: Patients with primary brain tumors and treated without Hippocampal Sparing Radiation Therapy Using 3DCRT technique.

Conformal radiation plan was planned for patients in both groups. The hippocampus was contoured according to contouring atlas - RTOG 0933. Hippocampal avoidance regions were created using a 5- mm volumetric expansion around the hippocampus to spare the subgranular zone of the hippocampus during cranial irradiation. The individually contoured hippocampus was used as a dose-limiting structure (<30Gy).

In both arms Adjuvant or Definitive brain radiotherapy via LINAC was delivered typically with a dose of 54Gy/27fractions (WHO grade II) to 59.4 Gy/ 60 Gy (WHO grade III/IV) depending on the histology and grade of the tumor, over a period of 5 to 6 weeks.Patients in both the groups received concurrent Temozolomide 75mg/m2 & adjuvant Temozolamide of 150-175mg/M2 5days/month for 6 months.Patients were assessed and compared for Memory function with validated questionnaire of Hopkins Verbal Learning Test (HVLT) in both the groups after completion of RT at 2 months, 4 months and 6 months[9].

Statistical analysis

All the demographic variables was represented using mean and standard deviation. Descriptive data was expressed in numbers and percentages. Independent sample t test will be performed to compare mean values amongst groups. Comparison of the number of samples amongst groups was carried out by Chi-square test.

Results

Uniform age distribution was noted among patients in both the arms .With 79.41% of the patients in the age group of 21-60years.Central nervous system tumours have a male predominance and the same was observed in our study with a total of 23 patients out of 34 being

male (67.64%). All patients in this study had an ECOG –Performance score of 0- 1 with 26 out of 34 patients (76.47%) having a score of 1.Primary brain tumors are usually associated with neurological deficits.Majority of the patients (25 out of 34patients) had no deficits 4 patients had seizures in the IMRT group 1 patient each showed involuntary movement and hemiparesis in 3D-CRT group. 1 patient each showed involuntary movement, loss of vision and hemiparesis in the IMRT group.

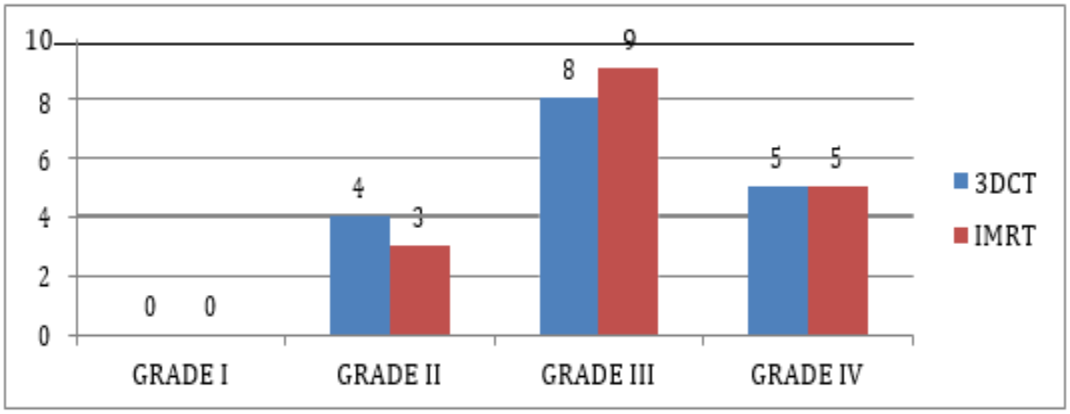

FIGURE 1 - WHO GRADING

The most common tumourlocation was the Fronto-parietal region where 6 patients were treated in the 3D-CRT arm and 3 patients in the IMRT arm. The least commonly involved sites were the tentorial and occipital region.Patients in this study ranged from WHO Grade II – IV. Maximum number of patients belonged to Grade III (n=8(47.06%)-3D-CRT arm: n=9(52.94%) in IMRT arm. WHO Grade IV tumours were equally distributed in both the arms.In our study , patients with various histology's were enrolled with the Most common type being the GlioblastomaMultiforme type with 6 patients (35.29%) in the IMRT arm and 5 patients (29.41%) treated in the 3D-CRT arm [10].

Least common types seen with 1 patient each was Anaplastic Astrocytoma and Oligodendroglioma.

TABLE 1 - HISTOPATHOLOGICAL DIAGNOSIS

DIAGNOSIS	3D-CRT	IMRT
Anaplasticastrocytoma	3(17.65)	3(17.65)
Anaplasticoligodendroglioma	4(23.53%)	1(5.88%)
Anaplasticoligoastrocytoma	0	1(5.88%)
Anaplaticependymoma	1(5.88%)	1(5.88%)
Menigioma	2(11.765%)	3(17.65%)
Glioblastomamultiforme	5(29.41%)	6(35.29%)
Oligoastrocytoma	2(11.765)	1(5.88%)
Oligodendroglioma	0	1(5.88%)
Total	17	17

The patients in this study were treated with Radiation dose of 54Gy – 60Gy depending on the histology and the grade of the tumour.In our study, Hippocampal sparing in the IMRT arm helped in achieving a lower mean hippocampal dose, of 21.94 ±2.44Gy compared to a dose of 27.06 ± 3.51Gy(p value – 0.00001) in the 3D-CRT arm , in the ipsilateral side of the tumor . The mean contralateral hippocampal dose in the 3D-CRT & IMRT group was found to be 16.24 ± 2.95 and 14.29 ± 1.99, which was found to be statistically significant.

TABLE 2 - RADIATION DOSE DISTRIBUTION

DOSEDISTRIBUTION	3D-CRT	IMRT
54Gy	4(23.53%)	3(17.65%)
59.4Gy	6(35.29%)	8(47.06%)
60Gy	7(41.17%)	6(35.29%)
TOTAL	17	17
	Chi – 0.505	**P– 0.777**

The mean Hopkins score before RT was in the same range before the start of Radiation therapy in both the arms. At 2 monthspost radiation – the score was 10.65±0.79 in the 3D-CRT arm with a marginally higher score in the IMRT arm 11.24 ±075. The mean Hopkins score at 4 months – post radiation therapy ,the score in IMRT arm was 11.06 ± 0.83 which was slightly better than the assessment for patients in the 3D-CRT arm .(9.94 ±1.25).This was statistically significant with a p value of 0.0021. The mean Hopkins score at 6 months interval in the 3D-CRT & IMRT group was found to be 10.18 ± 1.01and 10.82 ± 0.95, which was found to be statistically significant with the p value of 0.032.

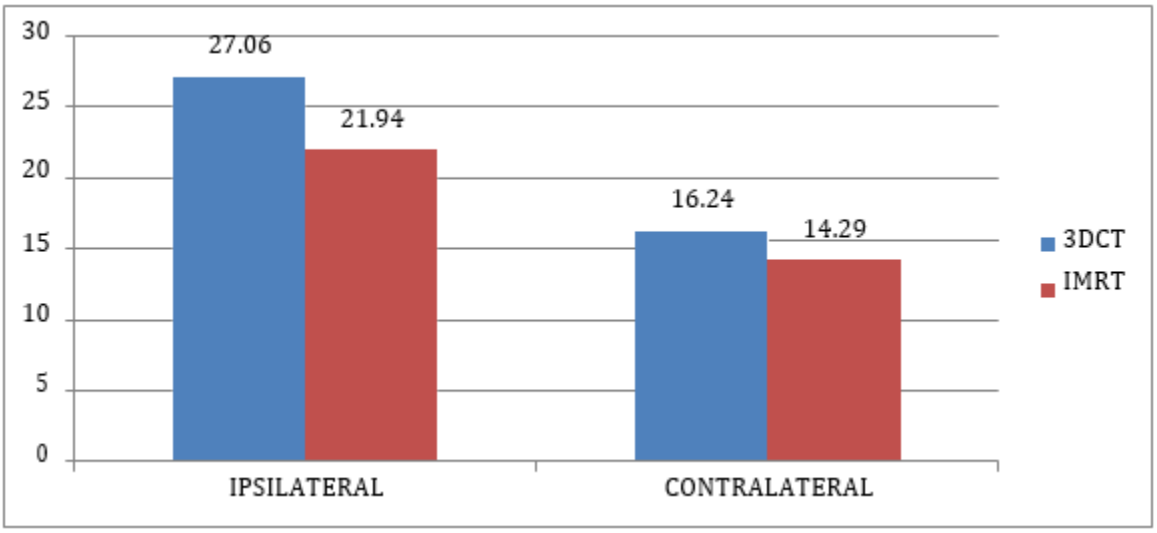

FIGURE 2 - HIPPOCAMPUS DOSE DISTRIBUTION

TABLE 3 - HIPPOCAMPUS DOSE DISTRIBUTION AMONGST GROUPS

DOSE DISTRIBUTION(Gy)	3D-CRT	IMRT	Pvalue
IPSILATERAL	27.06 ± 3.51	21.94 ± 2.44	**0.00001**
CONTRALATERAL	16.24 ± 2.95	14.29 ± 1.99	**0.015**

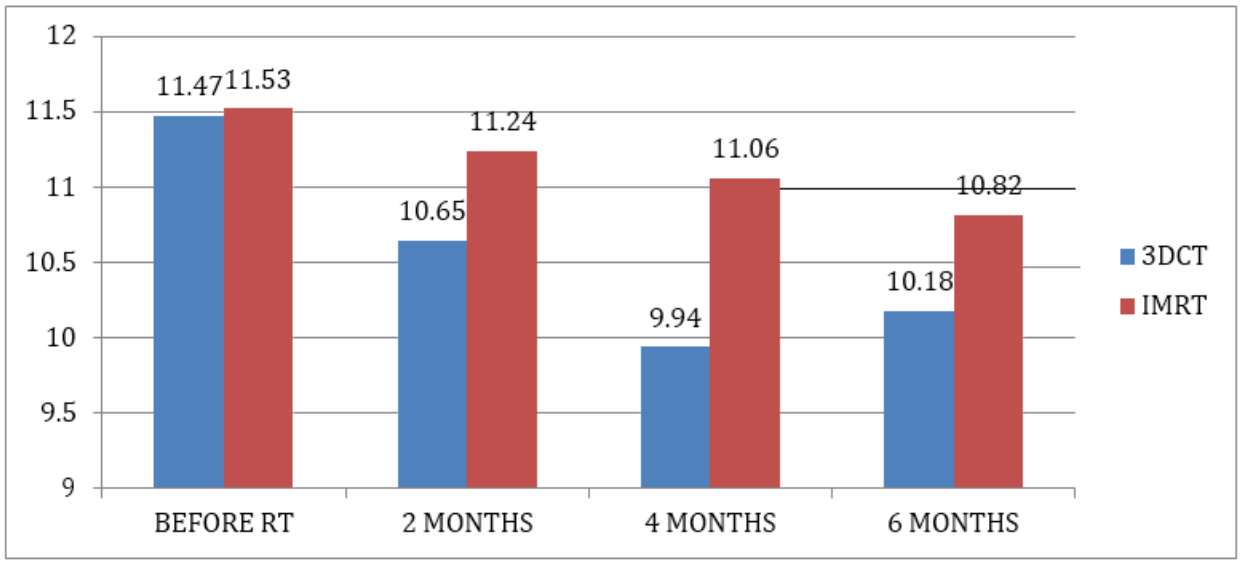

FIGURE 3 - HOPKINS SCORE

Discussion

In patients with gliomas that are expected to survive for many years, the potential deleterious effects of treatment should be minimized. Cranial irradiation for primary brain tumours has been associated with deficits in hippocampal-dependent functions such as learning, memory and spatial information processing[11]. Radiation when directed towards the hippocampus substantially causes neurocognitive decline as it plays an important role in the consolidation of information from short-term memory to long term memory and spatial navigation. Hence, sparing of the hippocampus is important to limit the after effects especially dementia. Over time newer treatment modalities like IGRT, IMRT, 3DCRT have come up to aid in preventing neurocognitive decline and therefore improving the patient's Quality of life. In our study we have used 3DCRT &IMRT as treatment modalities in the management of brain tumors[12].

For our study we enrolled 34newly diagnosed, histologically proven patients, and observed that there was uniform age distribution in both the arms with majority of the patients falling between the age group of 21-60 years with male predominance in both the arms.HistopathologicallyGlioblastomamultiforme(GBM) was the most common primary tumor followed by anaplastic astrocytoma in our study. The most commonly involved cerebral site in both the groups were fronto- parietal, frontal, fronto-temporal, temperoparietalregion [13].

As all the patients in either group were having an ECOG score of 0 and 1, the results were highly favorable and competent as per their performance scale rating and did not require any ambulatory support or be dependent on others for supportive care. Majority of patients with primary brain tumours usually present with Neurological deficits .In our study Seizures was the most common neurologicaldeficit, seen among 4 patients in our study at the time of diagnosis. About 88.23% of the patients in the 3D-CRT and 58.82% in the IMRT group did not show any neurological deficits. 1 patient each showed involuntary movement and hemiparesis type of neurological deficit in the 3D-CRT & the IMRT group. Loss of vision was noted in 1 patient

WHO Grading of the tumor at the stage of diagnosis not only provided us with a universal diagnosis but also helped in deciding the dose of radiation to be delivered as well as planning and providing the accurate treatment.

In a study done by Pinkham MB et al., the median dose prescribed was 59.4Gy in 33 fractions and 11 patients had WHO grade III gliomas.In another study done by, the mean dose to the contralateral hippocampus was 24.9Gy showing that hippocampal-sparing radiotherapy is feasible in a majority of patients with WHO grade II and III gliomas using IMRT7. In a study conducted by Gondi et al48 where combination of two computerized Cogstate tests (i.e., International Shopping List Test, One Card Learning Test) with the HVLT in the RTOG 0933 trial examining the ability to preserve neurocognitive function with the use of HA-WBRT demonstrated a dramatic reduction in memory decline as measured by the HVLT compared to a historic control [14,15 and 16].

We conducted memory assessment with the Hopkins verbal learning test, in each type of treatment modality (3D-CRT & IMRT group), followed in our study to understand the effects of radiation on the memory status of the individual [17].

The mean Hopkins score at 6 months interval in the 3D-CRT & IMRT group was found to be 10.18 ± 1.01and 10.82 ± 0.95, which was found to be statistically significant with a p value of 0.032.It was hypothesized that minimizing radiation dose to the least possible level in hippocampal region might delay or reduce the onset, and/or severity of neurocognitive deficit. Tome et al [18]. from their study proved that conformal avoidance of hippocampus is associated with preservation of memory and QAL as compared to the historical study group shows the efficacy of IMRT as a treatment modality as well its effectiveness at a lower dosage.

Conclusion

We hereby conclude that, there is a significant benefit to the use of IMRT technique for hippocampal sparing in Primary brain tumours, in terms of preventing neuro cognitive decline and reduced mean hippocampal dosage .Neurocognitive benefit was seen in most patients even after 6 months of follow up post irradiation.

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