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Hippocampal avoidance whole brain radiotherapy in brain metastasis using volumetric modulated arc therapy: experience from a Regional Cancer Centre of Eastern India

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ABSTRACT

Background: Whole-brain radiotherapy is associated with neurocognitive decline and decreased quality-of-life (QOL) among survivors of brain metastasis. Hippocampal-avoidance whole-brain radiotherapy (HA-WBRT) has shown advantage in delaying or preventing the neurocognitive decline while maintaining disease control. This study was done to assess the benefits and feasibility of HA-WBRT in patients with cerebral metastasis in terms of preservation of neurocognitive function and quality of life.

Materials and methods: 27 patients with brain metastasis treated by HA-WBRT and having the records of detailed neurocognitive-assessments were analysed from the database of our hospital. The patients were treated with HA-WBRT to a total dose of 30 Gy in 10 fractions with LINAC based IMRT using the VMAT technique. Cognitive function assessment was carried out using "Examination of the Cognitive Functions" scale provided by Bangur-Institute-of-Neurosciences, Kolkata, 2 weeks prior to radiotherapy and post-treatment two-monthly up to 6 months followed by every 3 months till the last follow up. QOL was assessed at the same interval using the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR). Follow-up was done till the date of death.

Results: Mean relative cognitive decline percentage decreased over subsequent follow-up visits and was 13% (SD ± 6%), 5% (SD ± 5%), 5% (SD ± 9%) and 2% (SD ± 12%) at 2 months, 6 months, 9 months and 12 months, respectively ($p \leq 0.05$). Statistically significant improvement was seen in the mean social-wellbeing (SWB) parameter of QOL (8%. ± 13%, 12%. ± 16%, 7%. ± 20%, no change at 2 months, 4 months, 6 months and 9 months, respectively) ($p \leq 0.05$). Mean relative decline in the Emotional-Well Being (EWB) parameter was significant only at 12 months and was 20% (SD ± 35%) ($p = 0.04$). Mean FACT-BR total Score showed a slight decrease till 9 months from baseline, and then showed a slight improvement up to 12 months.

Conclusion: HA-WBRT is feasible with LINAC-based IMRT using the VMAT technique and beneficial to the patients in preserving neurocognitive function and quality of life without compromising disease control.

Key words: brain metastases; hippocampal sparing WBRT; cognitive functions

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Introduction

Metastatic brain tumors are the most common brain tumors in adults affecting up to 30% of cancer patients. Over the past four decades population-based studies have suggested an incidence rate of approximately 10 per 100,000 population [1–6].

Definitive treatment options for brain metastasis include surgery, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). By the 1970s, WBRT had become a mainstay treatment for cerebral metastases [7], and while some of its uses are now being supplanted by stereotactic radiosurgery, it remains a beneficial adjunct to other therapies, is used as monotherapy in a variety of clinical situations and is still the treatment of choice in patients with widely disseminated metastases in the brain. However, the main concern regarding the usage of WBRT is the possibility of developing long term neurocognitive deficits (particularly learning and memory) among the treated patients [8].

The hippocampus is the most critical brain structure involved in episodic memory processing [9, 10]. It has been shown in many studies that there are neural stem cells located in the subgranular zone of the hippocampal dentate gyrus [11, 12]. These cells are radiosensitive and damage to these cells is central to the pathogenesis of memory decline after whole brain radiotherapy. Preliminary results from a recent MD Anderson study of low-grade or anaplastic brain tumors treated with radiotherapy have observed a dose-response phenomenon, where the maximum radiation dose to the left hippocampus was correlated with subsequent decline in learning ($p = 0.014$) and delayed recall ($p = 0.01$) [13].

Various other clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in the cognitive decline of patients. In particular, deficits in learning, memory, and spatial processing observed in patients who have received WBRT are thought to be related to hippocampal injury [14, 15]. Deficits in memory are strongly correlated with and precede decreased quality of life [16] and, thus, play an important role in subjective well-being of patients. Newer and more aggressive treatment approaches have demonstrated survival benefit in subpopulations of patients with brain metastases [8]. In this context, neurocognitive function (NCF) and quality-of-life (QOL) issues have become important concerns for "patients surviving after WBRT" and for patients receiving prophylactic cranial irradiation for small cell lung cancer as whole brain radiotherapy has been hypothesized to be associated with decline in neurocognitive function, specifically memory (delayed recall).

To prevent radiation induced loss of neuronal stem cells, hippocampal sparing radiation techniques have been developed and data from helical tomotherapy or linac based intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) have proven the feasibility of the approach. Hippocampus avoidance-WBRT (HA-WBRT) may prevent hippocampal damage and attenuate cognitive decline as measured by standardized neuropsychological testing. The NRG Oncology CC001 phase III randomized trial investigating WBRT and memantine hydrochloride versus HA-WBRT and memantine hydrochloride recently showed a significantly lower risk of neurocognitive failure in the HA- WBRT arm compared to conventional WBRT arm [17]. The avoidance of the hippocampus during WBRT is considered to be a safe treatment concept, with a rate of (peri)hippocampal disease progression after HA-WBRT, according to previous data, between 7.6 and 12.1% [18–19].

Gondi et al. [20] published the results of the RTOG0933, a single-arm phase II study that demonstrated that avoidance of the hippocampus during whole brain radiotherapy is associated with preservation of quality of life and memory. In this series, 100% of the hippocampus could not exceed 9 Gy, and maximal hippocampal dose could not exceed 16 Gy in 10 fractions. Based on the above findings, modern IMRT techniques have been developed to avoid conformally the hippocampal neural stem-cell niche during WBRT, often referred to as HA-WBRT [21, 22]. These techniques have demonstrated the ability to reduce mean dose to the neural stem-cell compartment by at least 80%, while providing acceptable coverage and dose homogeneity to the remaining whole-brain parenchyma [22].

Mean dose guidelines for HA-WBRT were first published by Gondi [20]. HA plans were compared with standard WBRT ones where a homogenous dose 30 Gy was applied to the whole brain including hippocampus. For HA plans, the median hippocampal dose achieved was 5.5 Gy (Dmax 12.8 Gy) and 7.8 Gy (Dmax 15.3 Gy) for helical tomotherapy

and LINAC based RT, respectively. These dose reductions have been considered a reference for other subsequent planning studies.

From the above studies it is evident that it is now technically and dosimetrically feasible to implement Hippocampal avoidance approaches into clinical practice. Numerous studies have addressed the issue of HA-WBRT but most of the data are from western countries and there are limited literatures and paucity of data on Indian population, specifically Eastern India.

In the present study, whole brain radiotherapy was used to treat patients of brain metastases with linac based with the VMAT technique using conformal avoidance of bilateral hippocampus and patient's quality of life and neurocognitive functions were evaluated before and after the completion of treatment.

This study reports whether there is prevention of radiation induced neurocognitive decline, specifically memory recall and preservation of quality of life, following hippocampal sparing whole brain radiotherapy.

Materials and methods

We undertook this retrospective observational study at the Chittaranjan National Cancer Institute (CNCI), Kolkata, which is one of the Regional Cancer Centres of Eastern India. The treatment records of patients of brain metastases (registered at the hospital between 2015–2019) referred to the Department of Radiation Oncology were analysed from the hospital database. A total of 27 patients of brain metastasis based on radiological diagnosis with histologically diagnosed primary who were treated with whole brain radiotherapy using IMRT (with VMAT technique) with a dose of 30 Gy in 10 fractions with hippocampal avoidance were included in the study. As per records, in all patients, dexamethasone was administered at loading dose of 10–20 mg for initial symptom control followed by doses of 4mg four times a day along with a concurrent proton pump inhibitor. Steroids were tapered as early as possible to minimize side effects. The data regarding Cognitive function assessment and Quality of Life were collected and documented in the patient records during follow-ups.

The patients were aged between 35 and 70 years, Karnofsky performance score 70 and above, normal renal function, liver function and blood counts. RPA class 1 or 2 were only included in the study. Due approval of the institutional ethical committee was obtained before analysing their data.

For CT Simulation, Patients were immobilized in a supine position with a thermoplastic 3 clamp mold over the head with an appropriate neck rest. A non-contrast planning CT scan of the brain (Slice thickness of 1.5 mm) was taken from skull vertex to C7 vertebra.

Gadolinium enhanced T1-weighted axial MRI images of the brain of slice thickness 1.5mm were taken for accurate contouring of the hippocampus. These image sequences were obtained with the patient in a supine position.

The MRI for radiotherapy planning and the planning CT were fused for hippocampal contouring with the help of auto fusion.

The clinical target volume (CTV) was defined as the whole brain parenchyma to C1 if there is no posterior fossa metastasis or C2 if there is posterior fossa metastasis.

The planning target volume (PTV) was drawn by taking 0.5 cm margin from the CTV.

All the patients had measurable brain metastasis outside a 5 mm margin around either Hippocampus. Hippocampal avoidance zone was subtracted in order to create PTV.

Hippocampal contouring was done following the guidelines provided by RTOG0933 contouring atlas.

Bilateral hippocampus was contoured as right and left hippocampus and a hippocampal avoidance zone was created using a 5 mm volumetric expansion around bilateral hippocampus.

WBRT was administered using the VMAT technique with image guidance using cone beam computed tomography (CBCT) on Elekta Synergy Linear Accelerator (Elekta, Stockholm, Sweden) with treatment planning on Monaco 3-DTreatment Planning System (Elekta, Stockholm, Sweden).

VMAT dose prescription*

PTV 30 G 10#
Bilateral hippocampus Dmax < 8–9 Gy
Bilateral hippocampal prv Dmax < 12–16 Gy
Bilateral lenses Dmax < 10 Gy

***Reference:** QUANTEC (Qualitative Analysis of Normal Tissue Effects in the Clinic) and RTOG CONSENSUS

All plans were done by using three arc beams. One full arc (360 degrees) with zero degree couch angle and two partial arcs of 150 degree each with couch angles of 45 degree and 315 degree were used.

Particular plan was approved if Volume receiving 30 Gy or higher (V30) was ≥ 90% and dose to 2% of the PTV (D2%) ≤ 40 Gy.

Dose volume histograms as well as isodose distributions on every single slice were evaluated carefully before final approval of plan.

Approved plans were sent to Mosaiq (record and verification system for treatment delivery).

On the first three days of EBRT, patients' positions were verified daily with X-ray volumetric imaging (XVI Release 5.0.2 b72)/cone beam CT and then twice weekly during the course of treatment to check the reproducibility of patient set-up.

Cognitive function assessment

Cognitive function assessment was carried out using "Examination of the Cognitive Functions" scale provided by the Cognitive and Behavioral Neurology Clinic, Bangur Institute of Neurosciences, Kolkata. It was very easy to use and was easily understood by the patients. Time to administer was 5 minutes.

The test involved memorizing a list of 10 targets for 3 consecutive trials (immediate recall), identifying the 10 targets from a list of semantically related or unrelated items (immediate recognition), and recalling the 10 targets after a 20-minute delay (delayed recall). Each patient served as his/her own control, as the difference in scores obtained at baseline and at pre-specified post-treatment intervals were calculated.

Cognitive Assessment Score (Delayed Recall)% Retained was calculated as follows:

(Trial 4 Result/Highest of Trial 1 – 3) × 100%

Relative decline at month Mi was defined as (BS0 — SMi)/BS0 where BS0 was the baseline score and SMi is the score at month Mi from baseline measurement date. [Mi — follow-up measurement of cognitive function; Smi — "Subsequent" or "Second" follow-up measurement of cognitive function].

Mean relative decline was measured as the mean of all observations on month Mi. Mean relative decline has been measured for both cognitive assessment and quality of life.

Quality of life was assessed using the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR). FACT-BR total score was calculated as the sum of scores from the five scales and has a possible score range of 0–200.

Patients were assessed about 2 weeks prior to start of radiation therapy. The measured assessment was referred as baseline parameters. The first post treatment assessment was done at 2 months from baseline and thereafter every 2 months till 6 months followed by every three months till the last follow up.

Apart from cognitive assessment and quality of life assessment, contrast enhanced MRI was obtained every 2 months from baseline for the first 6 months, and every 3 months thereafter to see if there is any increase in perpendicular bidimensional tumor area for any of the brain metastases, or the appearance of any new brain metastasis. Follow up was done till the date of death.

Statistical analysis

Statistical analysis was performed with help of Epi Info (TM) 3.5.3.

Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (SD). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi-square (χ^2) test was performed to find the associations. Kaplan-Meier survival analysis was performed to find the cancer specific survival of the patients. $p < 0.05$ was taken to be statistically significant.

Results

This study analyzed 27 patients with brain metastases who received HA-WBRT. Among them 13, patients had breast cancer (invasive ductal carcinoma) and 14 patients had adenocarcinoma lung**.** 21 patients (77.8%) had oligometastases whereas 6 patients (22.2%) had multiple metastases (median number of brain metastasis was 2 in both cohorts). All the patients received palliative WBRT with the dose of 30 Gy in 10 fractions over two weeks and all of them completed the treatment, and it was possible to assess the cognitive functions. Neurocognitive function assessment,

Table 1. Baseline parameters (before treatment) of the patients

Baseline parameters	No (%)
Age (in years)	
35-44	4 (14.8)
45-54	12 (44.5)
55-64	11 (40.7)
Sex	
Male	12 (44.4)
Female	15 (55.6)
Primary site	
Breast	13 (48.1)
Lung	14 (51.9)
Histology	
Adenocarcinoma	14 (51.9)
Invasive ductal carcinoma	13 (48.1)
No of brain metastasis	
Oligometastasis	21 (77.8)
Multiple metastasis	6 (22.2)
RPA class	
1	17 (63)
2	10 (37)
Baseline Mean Cognitive Assessment Score and Mean Quality of Life [Mean ± SD]	
Cognitive Assessment Score (Delayed recall) % Retained	0.86 ± 0.04
Quality of life parameters	
Physical well-being (PWB) [0–28]	13.70 ± 3.79
Social/family well-being (SWB) [0–28]	17.67 ± 2.80
Emotional well-being (EWB) [0–24]	9.74 ± 2.41
Functional well-being (FWB) [0–28]	9.52 ± 3.42
Brain Cancer Subscale (BrCS) [0–92]	54.74 ± 7.01
FACT-BR Total Score [0–200]	105.37 ± 9.74
Total duration of therapy (in days) (from start date to end date)	12.52 ± 0.89

SD — standard deviation; FACT-BR — Functional Assessment of Cancer Therapy with Brain Subscale

specifically delayed memory recall, and quality of life assessment were done for all the patients before and after completion of treatment till the last follow up. Follow up was done at 2 months, 4 months, 6 months, 9 months, 12 months and 15 months from baseline. Only 1 patient was alive during subsequent follow up done after 12 months and, therefore, the mean Cognitive Assessment Score and Quality of Life could not be assessed at 15 months. Follow-up MRI done at regular interval showed intracranial disease progression in 6 patients, partial response in 13 patients, complete response in 8 patients (according to RECIST1.1). However, none of the patients had progression in hippocampal avoidance zone. No documented ≥ Grade 3 neurological toxicities related to WBRT were observed.

Table 2. Cognitive function parameters in hippocampal-avoidance whole-brain radiotherapy (HA-WBRT) (% Retained)

Mean Cognitive Assessment Score (Delayed recall) % Retained	HA-WBRT [Mean ± SD]
2 months from baseline (n = 27)	0.75 ± 0.06
4 months from baseline (n = 24)	0.78 ± 0.07
6 months from baseline (n = 19)	0.82 ± 0.04
9 months from baseline (n = 13)	0.82 ± 0.07
12 months from baseline (n = 6)	0.82 ± 0.06

SD — standard deviation

Table 3. Cognitive function parameters in hippocampal-avoidance whole-brain radiotherapy (HA-WBRT) (% Declined)

Cognitive Assessement Score (Delayed recall) (in %): Mean Relative Decline	HA-WBRT [Mean ± SD]
2 months from baseline (n = 27)	0.13 ± 0.06
4 months from baseline (n = 24)	0.09 ± 0.09
6 months from baseline (n = 19)	0.05 ± 0.05
9 months from baseline (n = 13)	0.05 ± 0.09
12 months from baseline (n = 6)	0.02 ± 0.12

SD — standard deviation

Cognitive function assessment

At the assessment done at 2 months from baseline, all 27 patients, were alive and the mean Cognitive Assessment Score (Delayed recall)% Retained was 75% as compared to the baseline value of 86%.

At 4 months from baseline, 24 patients were alive and were assessed. Mean Cognitive Assessment Score (Delayed recall)% Retained was 78% as compared to the baseline value of 86%. Mean rela-

Table 4. Quality of life parameters in hippocampal-avoidance whole-brain radiotherapy (HA-WBRT) (% Declined)

	Mean ± SD
Social/Family Well Being (SWB): Mean Relative Decline	
2 months from baseline (n = 27)	–0.08 ± 0.13
4 months from baseline (n = 24)	–0.12 ± 0.16
6 months from baseline (n = 19)	–0.07 ± 0.20
9 months from baseline (n = 13)	0.00 ± 0.17
12 months from baseline (n = 6)	0.02 ± 0.28
Emotional Well Being (EWB): Mean Relative Decline	
2 months from baseline (n = 27)	0.09 ± 0.23
4 months from baseline (n = 24)	0.05 ± 0.26
6 months from baseline (n = 19)	0.02 ± 0.29
9 months from baseline (n = 13)	–0.11 ± 0.31
12 months from baseline (n = 6)	–0.20 ± 0.35

SD — standard deviation

Table 5. Quality of life parameters in hippocampal-avoidance whole-brain radiotherapy (HA-WBRT) [Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) Total Score] (% Declined)

FACT-BR Total Score: Mean Relative Decline	HA-WBRT [Mean ± SD]
2 months from baseline (n = 27)	0.01 ± 0.04
4 months from baseline (n = 24)	0.02 ± 0.04
6 months from baseline (n = 19)	0.01 ± 0.05
9 months from baseline (n = 13)	0.01 ± 0.05
12 months from baseline (n = 6)	0.02 ± 0.04

SD — standard deviation

tive cognitive decline was 9% (SD ± 9%), p = 0.001. At 4 months, 12.5% patients showed preserved or improved cognitive functions and this was found to be statistically significant (p = 0.0002).

At 6 months from baseline, 19 patients were alive and were assessed. Mean relative cognitive decline was 5% (SD ± 5%), None of the patients showed more than 30% decline. It was also observed that there was statistically significant improvement (26.3%) in cognitive function (p < 0.0001).

At 9 months from baseline, 13 patients were alive and were assessed. Mean relative cognitive decline was 5% (SD ± 9%), 38.5% patients showed preserved or improved cognitive function.

At 12 months from baseline, only 6 patients were alive. Mean relative cognitive decline was 2% (SD ± 12%). 33.3% patients showed preserved or improved cognitive function.

Quality of life assessment

At 2 months there was 8% (SD ± 13%) improvement in mean social /family wellbeing (SWB) parameter. At 4 months there was 12% (SD ± 16%) improvement in mean SWB parameter. At 6 months there was 7% (SD ± 20%) improvement in mean SWB parameter. At 9 months there was no change in mean SWB parameter. At 12 months there was 2% (SD ± 28%) decline in mean SWB parameter. All of the results were statistically significant (p < 0.05). Mean relative decline in Emotional Well Being (EWB) parameter was significant only at 12 months and was 20% (SD ± 35%) (p = 0.04). Mean FACT-BR Total Score showed a slight decrease till 9 months from baseline, and then showed a slight improvement up to 12 months.

Cancer specific survival analysis

The mean cancer specific survival of the patient population was 263 ± 119.68 days (mean ± SD).

Discussion

There is an established role for WBRT in the management of multiple brain metastases. Though compelling, the dramatic reduction in the risk of subsequent development of brain metastasis with WBRT comes at the cost of potential neurocognitive toxicity [8]. A lifelong mitotically active and radiosensitive compartment of neural stem cells is located in the subgranular zone of the hippocampal dentate gyrus which has been associated with formation of new memory [23]. Injury to this neural stem-cell compartment has been hypothesized to be central

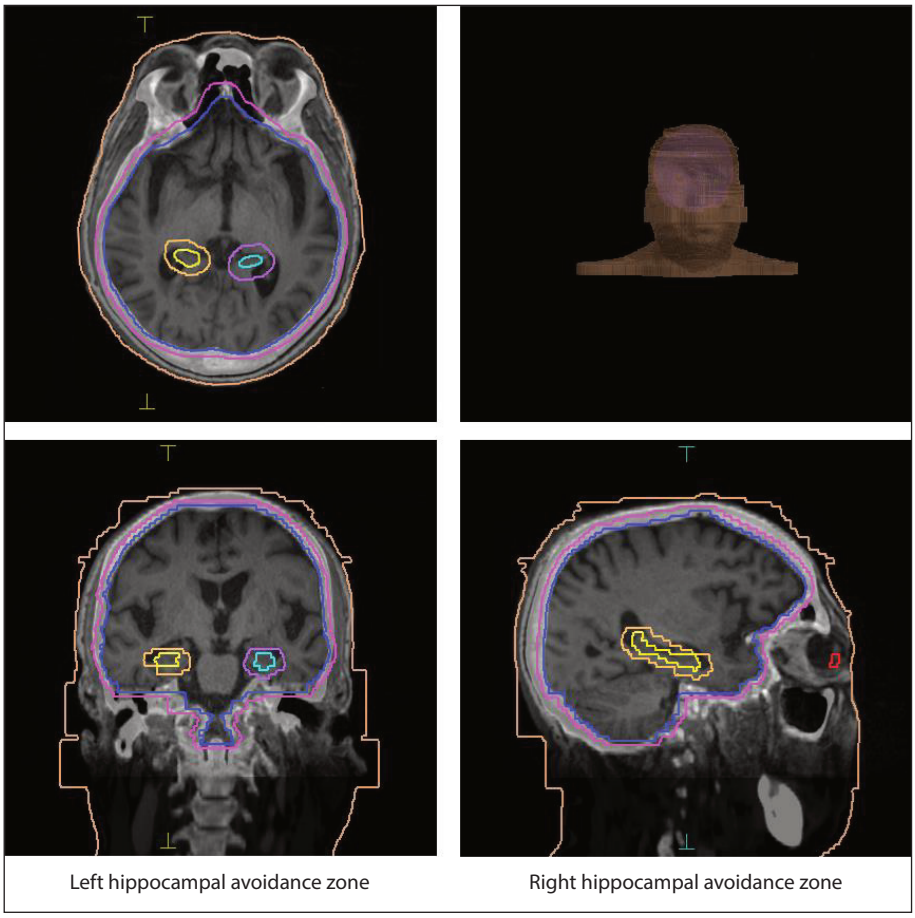

Figure 1. Magnetic resonance imaging (MRI) of the brain showing hippocampus in axial sections, the hippocampal avoidance zone in axial, coronal and sagittal sections. Source: TPS

to the pathogenesis of radiation-induced early cognitive decline [24].

Techniques have been developed to avoid conformally the hippocampal neural stem-cell niche during WBRT, often referred to as HA-WBRT with the help of IMRT. In this context the pioneer study was performed by Gutiérrez et al. in 2007, who tested feasibility of HA WBRT with simultaneous integrated boost (SIB) to Brain Metastasis in experimental radiotherapy plans using helical tomotherapy [25]. Regardless of a different setting of treatment plans (pitch and field width), no significant difference in hippocampal doses was described. It was concluded that it is possible to create combined plans with homogeneous whole brain dose distribution equivalent to conventional WBRT, while avoiding conformal Hippocampal and boosting radiosurgically equivalent dose to individual metastases. The study by Popp et al. also showed that HA-WBRT may effectively and durably minimize hippocampal damage compared to conventional WBRT, achieving a threefold reduction in atrophy over a time frame of 4 years following irradiation [26].

RTOG0933 study [20] which was an international multi-institutional single-arm phase II trial of HA-WBRT for brain metastases concluded that conformal avoidance of the hippocampus during WBRT is associated with preservation of memory and QOL as compared with historical series. The primary end point was Hopkins verbal learning test revised delayed recall (HVLT-R DR). Of 113 patients accrued, 42 patients were analyzable at 4 months. Mean relative decline in HVLT-R DR from baseline to 4 months was 7.0% [95% confidence interval (CI): −4.7% to 18.7%) which was significantly lower in comparison with the historical control 30% ($p < 0.001$). Only three patients (4.5%) experienced progression in the hippocampal avoidance area in the RTOG 0933 phase II HA-WBRT study [20] suggesting that HA-WBRT can be safely delivered to patients with brain metastases.

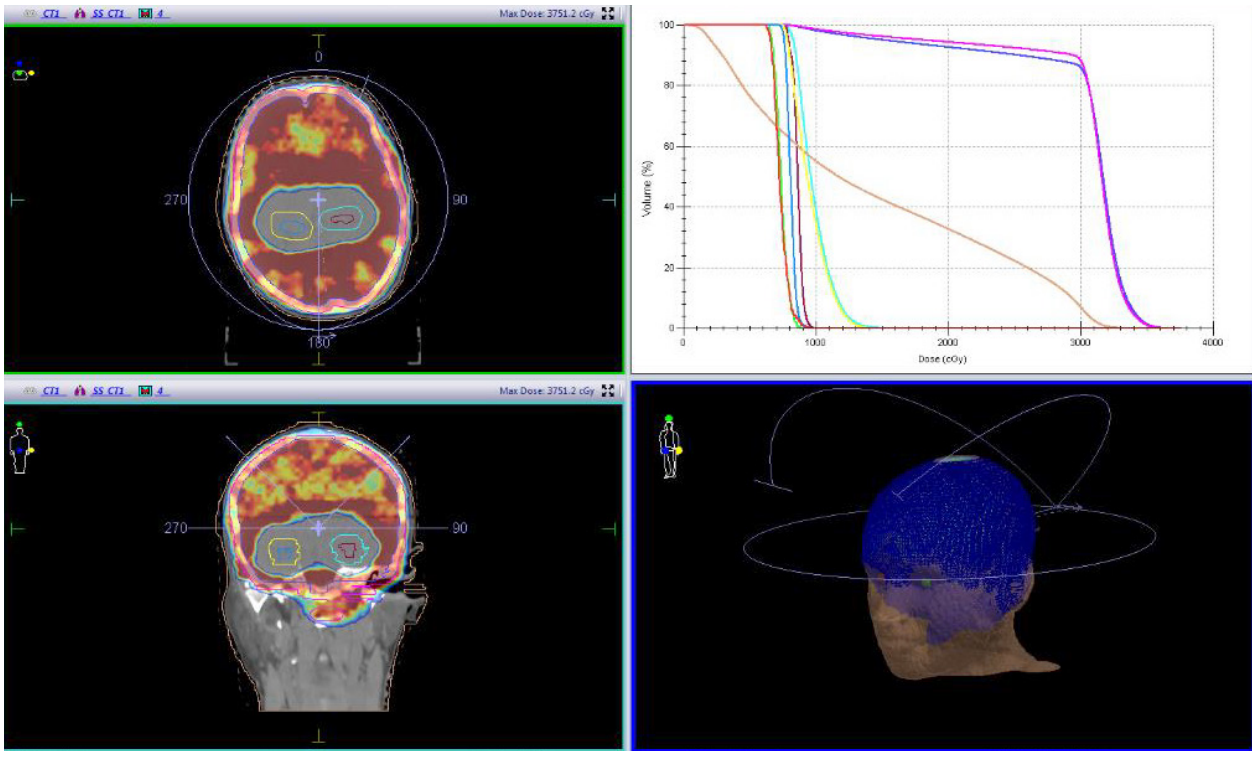

Figure 2. Beam arrangement with dose painting and dose-volume histogram (DVH). Source: TPS

In our study, data were analysed for the patients of metastatic brain tumors treated with intensity modulated radiation therapy (VMAT technique) with hippocampal avoidance to evaluate if there is prevention of radiation induced neurocognitive decline, specifically memory recall following hippocampal sparing.

At 2 months, mean relative cognitive decline was 13%. At 6 months from baseline, mean relative cognitive decline was 5% (SD ± 5%). At 9 months from baseline, mean relative cognitive decline was 5% (SD ± 9%). At 12 months from baseline, mean relative cognitive decline was 2% (SD ± 12%). It was observed that in patients in whom HA-WBRT was administered, mean relative cognitive decline percentage decreased over subsequent follow up visits and was statistically significant ($p < 0.05$). Therefore, hippocampal avoidance was associated with preservation of memory, especially delayed recall in patients receiving HA-WBRT. This supports the hypothesis that HA-WBRT prevented injury to the neural stem cells preserving neurocognitive functions.

Recent data from the NRG Oncology CC001 study suggested that cognitive failure can be effectively prevented by conformal sparing of the hippocampus. The NRG Oncology CC001 phase III randomized trial investigating WBRT and memantine hydrochloride versus HA-WBRT and memantine hydrochloride, has recently showed the use of HA during WBRT with memantine effectively sparing the hippocampal neuroregenerative niche to better preserve cognitive function and patient reported symptoms. No differences were observed in toxicity, intracranial PFS, or OS compared with standard WBRT and memantine [17]. In the present study preserved or improved cognitive function was observed in 12.5%, 26.3%, 38.5, 33.3% of patients at 4 months, 6 months, 9 months and 12 months, respectively ($p < 0.05$), which justifies the hippocampal sparing RT in this patient population.

The first large clinical trial in which neurocognitive assessments were studied in patients with brain metastases was PCI-P120-9801 which was a randomized phase III study [27]. 401 patients were enrolled and were randomly assigned to receive WBRT 30 Gy in 10 fractions with or without motexafin gadolinium 5 mg/kg/d. This study demonstrated that the combination of neurocognitive tests and tumor prognostic variables predict better survival than tumor variables alone. Addi-

tion of motexafin gadolinium to WBRT appeared to improve memory and executive function and prolong time to neurocognitive progression in patients with brain metastases from lung cancer patients. Quality of life monitoring was done regularly and Neurocognitive function and Quality of life were seen to be correlated in the patient population. The study suggested that delay in neurocognitive decline may help in preservation of quality of life in patients with brain metastases which, in turn, can lead to a better and improved overall patient care.

In a study showing relationship between neurocognitive function and quality of life after WBRT in patients with brain metastasis conducted at the Department of Human Oncology, University of Wisconsin Comprehensive Cancer Centre, Madison, WI 53792, USA [28] a total of 208 patients were analyzed. At baseline, all NCF tests showed statistically significant correlations with ADL, which became stronger at 4 months. A similar observation was made with FACT-BR. The study concluded that neurocognitive function and quality of life are correlated. Neurocognitive function deterioration precedes QOL decline. Thus, prevention of HVLT-R decline may represent one potential mechanism for the QOL preservation observed after HA-WBRT.

In our study statistically significant improvement was seen in the mean SWB parameter of quality of life (8% improvement, 12% improvement, 7% improvement, no change at 2 months, 4 months, 6 months and 9 months, respectively) ($p < 0.05$). At 12 months there was 2% (SD ± 28%) decline in the mean SWB parameter ($p < 0.05$). Mean relative decline in the EWB parameter was significant only at 12 months and it was 20% (SD ± 35%) ($p = 0.04$). Mean FACT-BR Total Score showed a slight decrease till 9 months from baseline, and then showed a slight improvement up to 12 months. It has been observed from literature that certain parameters of quality of life are affected by WBRT like social wellbeing and emotional wellbeing. So, by avoiding hippocampus during WBRT, certain parameters of quality of life can possibly be preserved. There has not been any reported statistically significant difference in the mean cancer specific survival between Hippocampal radiotherapy versus standard WBRT.

Supporting the hypothesis and evidence as reviewed in the literature [20], this study of HA-WBRT revealed decreased neurocognitive decline and improved neurocognitive function in HA-WBRT and improvement in certain parameters of quality of life.

Conclusion

Preservation of cognitive function and certain parameters of quality-of-life functions (SWB, EWB) were seen in HA-WBRT and were comparable to the findings in published literature [20]. However, there has not been any statistically significant difference in the cancer specific survival reported anywhere comparing standard WBRT. Larger randomized, preferably multi-institutional, studies examining the effects of HA-WBRT on neurocognitive functions and quality of life may be undertaken in near future.

Ethics approval and consent to participate

Due ethical approval and written informed consent from all the participants were taken for the study. Institutional Ethics Committee approval reference number- CNCI/ IEC Ref: A-4.311/62/2015.

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Conflict of interest

None declared.

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