

Hippocampal Sparing in Whole Brain Radiotherapy with Simultaneous Integrated Boost for Brain Metastasis – Feasibility and Neurocognitive Function Assessment

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Abstract

Introduction: Whole Brain Radiation Therapy (WBRT) is a standard in most of patients with brain metastasis. Hippocampus is being recognized as organ at risk to maintain neurocognitive functions and hippocampal sparing WBRT has been started. Further, WBRT followed by Boost shows better local control compared with WBRT alone. The present study is done to evaluate the feasibility of sparing the hippocampus and assessment of neurocognitive function treated with WBRT with boost in brain metastasis.

Materials and Methods: All patients with brain metastasis were recruited and followed between December 2022 and January 2025. Inclusion criteria: Pathologic proven diagnosis of solid tumor malignancy; Age ≥ 18 ; KPS ≥ 70 ; Mini Mental State Examination (MMSE) ≥ 18 ; RPA class I or II; One or more brain lesions. Exclusion Criteria - Previously treated patients of brain tumors or leptomeningeal disease by MRI and/or cerebrospinal fluid cytology. Baseline and follow up (at 0,3 and 6 months) neurological cognitive functions were assessed using Mini-Mental State Examination (MMSE) and Hopkins Verbal Learning Test-Revised (HTLV-R). Patients underwent radiotherapy with hippocampal sparing with dose fractionation of 30Gy to the whole brain-PTV (PTV30) and 45Gy to the boost-PTV (PTV45) using simultaneous integrated boost in 10 fractions. Dosimetric parameters of PTV and OARs were assessed. Statistical analysis was analysed using unpaired t-Test: two – samples of unequal variances, to calculate level of significance ($P < 0.05$ taken as significant).

Results: 23 patients with brain metastasis were recruited and followed. The mean age 55.34 years and seen more in females (sex ratio 1:1.9). Common primary sites were lung (43.47%) followed by breast (26.08%) with headache (73.9%) as commonest clinical presentation. The metastatic lesions were more common in supratentorial region (60.9%), commonest lobe being frontal (39.1%). Oligometastasis was seen in 91.3%. PTV dosimetry - Conformity index was 1.28 ± 0.34 and homogeneity index was 0.063 ± 0.021 . Dosimetric parameters of all OAR's were achieved except PRV Brainstem and Optic Chiasma in several cases. Hippocampal sparing achieved in 21 patients- Dmax 13.72 ± 1.84 Gy, Dmin 9.16 ± 1.5 Gy, Dmean 11.26 ± 2.08 Gy. Degree of impairment has no change in 17 patients in MMSE, ($p=0.52$) at 6 months and no significant decline or improvement in HVLt-R score from baseline.

Conclusion: Hippocampal sparing whole brain radiotherapy with simultaneous integrated boost can be an efficient therapeutic option for patients with brain metastasis to spare neurocognitive functions and may be associated with improved local tumor control.

Keywords: Brain metastasis, hippocampal sparing, whole brain radiotherapy, simultaneous integrated boost, neurocognitive function

INTRODUCTION

Whole Brain Radiation Therapy (WBRT) continues to be a standard quality of care in most of patients with brain metastasis. WBRT is well known for improving neurologic symptoms, with response rates ranging from 70% to 93%.¹ However, there is no consensus on the optimal dose and fractionation schedule for WBRT, and various schedules are postulated.

Recent developments in WBRT treatment planning and delivery strategies have spared vulnerable brain areas including the hippocampus, which was not previously recognized as an organ at risk.² Therefore, the use of WBRT with hippocampus sparing to maintain neurocognitive performance is not in common practice currently and is thought to be a novel concept with available literature.³⁻⁵

WBRT followed by Boost shows better local control compared with WBRT alone.^{6,7} While treating brain metastases, WBRT with simultaneous integrated boost (SIB) has been feasible due to variety of advance techniques, including volumetric arc therapy, intensity modulated radiation (IMRT), and helical tomotherapy.^{8,9}

While the tumor itself may affect the neurocognitive function (NCF) of patients, radiotherapy is also associated with declined NCF. In particular, due to the association between the hippocampal neural stem and memory function, radiation therapy of the hippocampal area is associated with deteriorated cognitive and memory functions.¹⁰⁻¹²

The concept of specifically avoiding the hippocampal region during brain radiation therapy emerged because contemporary radiotherapy methods like intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) enable the administration of extremely conformal dose distributions.¹³ The present study is done to evaluate the feasibility of sparing the hippocampus and assessment of neurocognitive function treated with WBRT with boost in brain metastasis.

MATERIAL AND METHODS

Twenty-three patients with brain metastasis were recruited and followed between December 2022 and January 2025

Study design: Prospective observational study

Sample Selection

Inclusion Criteria

Pathologic proven diagnosis of solid tumor malignancy; Age ≥ 18 ; KPS ≥ 70 ; Mini Mental State Examination (MMSE) ≥ 18 prior to study entry; RPA class I (KPS ≥ 70 , age < 65 , metastases in brain only) or class II (lack of one or more of class I criteria); One or more brain lesions.

Exclusion Criteria

Previously treated patients of brain tumors; Evidence of leptomeningeal disease by MRI and/or cerebrospinal fluid (CSF) cytology.

Study Tool

A pre designed pre tested questionnaire was used to access neurocognitive functions and clinical outcome. This questionnaire comprised of socio-demographic profile along with history & examination.

Neurocognitive Function Assessment Tests

Baseline neurological, cognitive function or quality of life test scores were assessed using the following tests: Mini-Mental State Examination (MMSE), Hopkins Verbal Learning Test-Revised (HVLT-R). They were done before starting of treatment (0 months), at 3-months & 6-month post completion of treatment.

Radiotherapy Planning (Fig 1a-f)

Immobilization, Image Registration, Contouring

All patients were immobilized using 3-point 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. Image registration is done and both the CT and MRI

slices are overlapped. CT Images were then being fused with MRI Images. Tumor appearance on T1-weighted MRI is similar to that on CT, although tumor volumes are better delineated on MRI. Treatment planning were optimized with MRI co-registration to assist in delineating gross tumor as well as adjacent organs at risk. Contouring is done on CT scan with overlapping images of MRI scan.

Target and OARs delineation

The entire brain parenchyma bounded inferiorly by the foramen magnum was expanded by 3 mm to form the whole brain-PTV. The gross tumor volume (GTV) was expanded uniformly by 3 mm to form the boost-planned tumor volume (boost-PTV).

The planning tumor volume of the brain (PTV whole brain) was defined as the whole brain plus 3 mm minus the planning tumor volume of gross metastases (PTV metastases). PTV metastases was formed by the addition of 3 mm to the gross tumor volume. Delineation of organs at risk (OARs) was done including the brainstem, optic chiasm, optic nerves, eyes, lens and hippocampus. The delineation of the hippocampus on the MRIs was based on RTOG 0933 delineation protocol.¹⁴ Expanded contours were created with safety margins of 3 mm around the brain stem & the chiasma.

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-hypo intense 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 begins 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 uncus 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 were terminated at the lateral edges of the quadrigeminal cisterns, prior to the emergence of the crus of the fornix. The hippocampal avoidance region was generated by expanding the hippocampal contour by 3mm volumetrically to account for necessary dose fall-off between the hippocampus and the PTV. Appropriate anatomical contouring was confirmed using T1-weighted MRI sagittal and coronal sequences. The PTV was excluding the hippocampal avoidance region, and lenses. Radiotherapy planning was done using opposed lateral fields or IMRT/VMAT technique with boost using IMRT or VMAT delivered sequentially.

Radiotherapy dose

The protocol of dose fractionation was 30Gy (BED=39Gy; EQD2=32.5Gy) to the whole brain-PTV (PTV30) and 45Gy (BED=65.25Gy; EQD2=54.37Gy) to the boost-PTV (PTV45) in 10 fractions. The whole brain-PTV was prescribed whole-brain dose, while the boost-PTV was prescribed a boost dose using a simultaneous integrated boost (SIB). The minimum coverage of both PTVs was 90% and 95% respectively, to be covered by prescription dose so as to achieve the required dose homogeneity (95-107%).

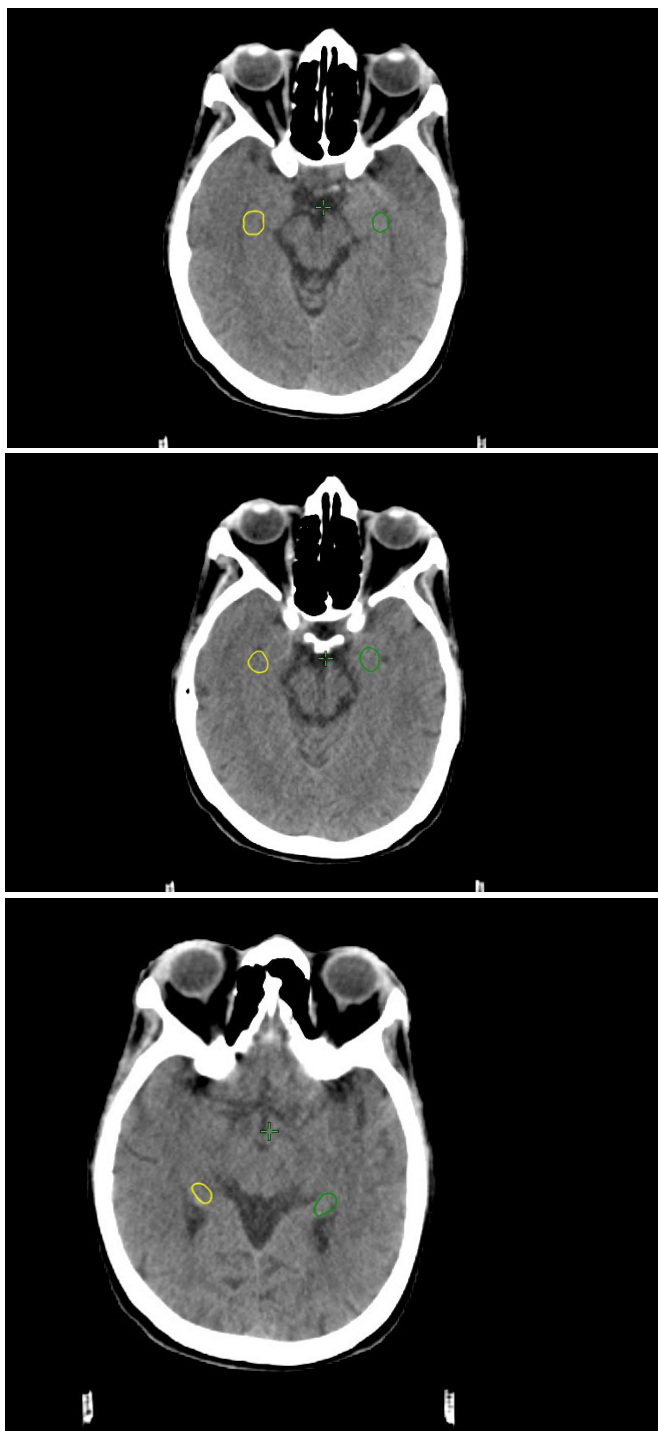


Fig 1 (a-c): Cranial to caudal CT-sections of hippocampus delineation (top to bottom)



Fig 1 (d). Axial CT section showing delineation of the organs at risk

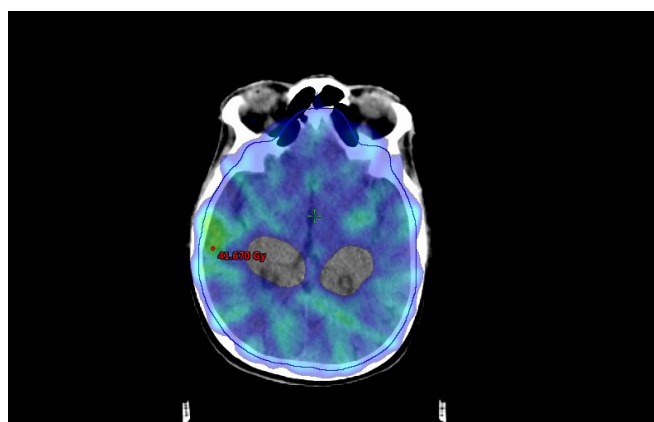


Fig 1 (e). Image showing hippocampus sparing dose wash of whole brain PTV (PTV 30)



Fig 1 (f). Image showing dose wash of metastasis (PTV 45)

Fig 1: Axial CT scans showing cranial to caudal hippocampus delineation (a-c), organs at risk (d), dose wash for PTV 30 (e) and dose wash PTV 45 (f)

Assessment of dosimetric parameters

- Dose–volume histograms (DVHs) corresponding to both the delivered plans for WBRT and Sequential Boost (Seq) were evaluated.
- All planning techniques were evaluated using dose-volume histogram (DVH). PTV dosimetric parameters for evaluation were as follows: PTV receiving 95% dose was designated as PTV (V95%), dose given to 95% and 90% of PTV will be designated as D_{95} and D_{90} respectively, 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% are representing the PTV volume. HI value closer to 0 indicates a homogeneous plan.
- The volume of other OARs receiving dose was quantified and these dosimetric parameters were designated as follows:
 - Hippocampus $D98\% \leq 9$ Gy, $D2\% \leq 17$ Gy, mean dose ≤ 10 Gy
 - Optic nerves, chiasm $D98\% \leq 33$ Gy
 - Optic nerve, 1-sided $D2\% \leq 35$ Gy
 - Retina, 1-sided $D2\% \leq 33$ Gy
 - Lenses $D2\% \leq 7$ Gy
 - Brain stem $D2\% \leq 33$ Gy

Radiotherapy techniques

IMRT/VMAT planning

- Coplanar multiple fields around isocenter using isotropic gantry angles were used and may be adjusted 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 were defined.
- Optimize fluence calculated for LINAC specification. Now the plan was evaluated by DVH.

Follow up

Patients were assessed weekly during Radiotherapy, at the end of radiotherapy and thereafter monthly up to 6 months. Neurocognitive function tests were done with multiple questionnaire at start of Radiotherapy and at 3 months and 6 months after Radiotherapy.

Ethical Considerations

This study was conducted after getting Ethical clearance certificate from Institute's Ethics Committee (Ref No. SRMS IMS/ ECC/2022/132).

Results and Observation

Results were tabulated or graphically reported to draw conclusion.

Data Analysis

Collected data was analyzed using standard statistical methods and software (unpaired t-Test: two – samples of unequal variances) to calculate level of significance using “p” value. “p” value of less than 0.05 is taken as significant in our study.

RESULTS AND OBSERVATIONS

Twenty-three patients with brain metastasis were recruited and

followed between 01/01/2023 to 31/01/2025. Patients were treated with IMRT or IGRT-VMAT technique and the dosimetric parameters of PTV and organs at risk including hippocampus were evaluated.

In our study group, the mean age of brain metastasis was 55.34 years, median age was 55 yrs and age range was 28 – 77 years. Maximum patients (30.4%) of brain metastasis fall in 61-70 yrs age group.

Brain metastasis more commonly seen in females than in males, with Male: Female ratio 1: 1.9.

The common primary sites for brain metastasis were lung (43.47%) followed by breast (26.08%). The other sites were endometrium, ovary, esophagus, stomach, gall bladder and lymphoma.

Commonest clinical presentation was headache (73.91%) followed by vomiting (21.7%), seizures (17.3%) and in lesser frequency (<10%) weakness of limbs and visual symptoms.

Details of metastatic lesions

Site

Supratentorial region (60.9%), infratentorial (8.7%) and both (30.4%)

Lobes of brain

Metastasis in brain are more commonly located in frontal lobe (39.13%), followed by fronto-parietal lobe (17.39%), and cerebellar region (13.04%). The lobes involved in lesser frequency (<10%) were temporal, occipital, parietal-occipital, temporal-parietal and fronto-parietal.

Number of brain metastasis

In the study, it was found that majority of the patients had single brain metastasis (56.52%) and number of lesions ranges from 1 to 10. Oligometastasis (1- 5) was seen in 91.3% and polymetastasis (6-10) in 8.69%.

Dosimetric parameters of PTV, hippocampus and OARs

In the present study, the mean Conformity index was 1.28 ± 0.34 and homogeneity index was 0.063 ± 0.021 (Table 1).

Out of 23 patients, Hippocampal sparing was achieved in 21 patients. The dosimetric parameters were $D_{max} 13.72 \pm 1.84$ Gy (16.9 – 11.22), $D_{min} 9.16 \pm 1.5$ Gy (13.76 – 8.34), $D_{mean} 11.26 \pm 2.08$ Gy (15.93 – 9.4). The 2 patients where Hippocampus sparing was not achieved, the dosimetric parameters were $D_{max} 32.22 \pm 0.82$ Gy (32.8 – 31.64), $D_{min} 29.98 \pm 0.98$ Gy (30.67 – 29.28), $D_{mean} 31.34 \pm 1.16$ Gy (32.16 – 30.51) (Table 2).

In the study, the dosimetric parameters of all the OAR's were achieved except PRV Brainstem and Optic Chiasma. In 14 cases dose to PRV brainstem was more than dose constraint prescribed ($D2\% \leq 33$ Gy), the mean dose being 35.54 Gy. In 17 cases dose to optic chiasma was more than dose constraint prescribed ($D98\% \leq 33$ Gy), the mean dose being 34.38 Gy (Table 3).

Neurocognitive Function Evaluation

Mini Mental State Examination Score (Table 4)

A score between 24-30 is no cognitive impairment i.e. Normal, 18-23 shows mild cognitive impairment, 0-17 depicts severe cognitive impairment. The mean value at 0 month is 21.73, at 3 months is 22.21, and at 6 months is 22.43. There is MILD neurocognitive

Table 1: Dosimetric Parameters of Boost PTV in patients of study group

S. No.	V95 (%) in cc	D95 (GY)	Dmax	Dmean	D2	D98	D50	CI	HI
1	5.76	45.45	49.22	47	48.22	44.94	47.11	1.58	0.06
2	10.6	43.42	46.64	44.51	45.48	42.64	44.61	1.67	0.06
3	7.5	44.77	47.46	45.88	46.96	44.51	45.91	1.68	0.05
4	22.34	44.72	48.94	46.14	47.38	43.97	46.26	1.22	0.07
5	35.62	43.05	47.7	44.91	46.2	41.98	45.11	1.07	0.09
6	33.46	42.91	47.04	44.87	46.19	42.47	45.09	1.03	0.08
7	12.49	44.56	47.51	45.47	46.58	44.22	45.49	1.59	0.05
8	91.4	44.16	46.26	45.06	45.81	43.59	45.13	0.88	0.05
9	25	43.84	47.38	45.24	46.42	43.28	45.32	1.17	0.07
10	13.5	42.98	49.74	46.53	48.66	43.43	46.73	0.82	0.11
11	6.9	44.66	46.36	45.51	46.11	44.31	45.58	0.62	0.04
12	50.8	43.04	47.94	45.14	46.67	41.61	45.38	1.08	0.11
13	2.1	44	46.28	44.96	45.89	43.85	45	1.71	0.04
14	47.6	46.39	49.07	47.41	48.24	45.85	47.51	1.32	0.05
15	16.8	44.53	48.39	45.57	47.32	44.3	45.51	1.68	0.06
16	16.2	45.2	47.77	46.29	47.09	44.84	46.41	1.33	0.04
17	25.7	43.37	48.24	45	46.59	42.85	45.16	1.13	0.08
18	5.8	46.28	48.59	47.34	48.17	45.87	47.41	1.56	0.04
19	36.7	45.35	48.26	46.54	47.39	44.81	46.68	0.78	0.05
20	58.5	44	47.23	45.42	46.25	43.43	45.6	1.1	0.06
21	19.4	43.71	48.25	45	46.79	43.22	45	1.2	0.08
22	18.09	44.29	48.77	46.07	42.78	43.77	46.2	1.65	0.08
23	23.9	44.37	46.37	45.19	45.96	44.19	45.23	1.73	0.04
Mean	25.48	44.3	47.8	45.69	46.65	43.82	45.8	1.28	0.063
SD	20.9	0.98	1.40	0.82	1.21	1.09	0.83	0.34	0.021

deficit noted. The p-value is 0.66 and 0.52 (at 3 and 6 months respectively) which is not significant ($p < 0.05$). Out of 23 study patients, Hippocampal sparing was achieved in 21 patients. The baseline neurocognitive impairment was mild in 16 patients, severe in 1 patient and rests 4 were normal. The degree of impairment has no change in 17 patients and improved to normal from mild category in 4 patients after 3 months of follow-up and remains same even after 6 months of follow up.

The 2 patients where Hippocampus sparing was not achieved, there was no change in neurocognitive functions after 3 and 6 month of follow-up.

Hopkins Verbal Learning Test-revised Score (Table 5)

The mean HVLTR score at 0 months is 19.47, at 3 months is 18.39, and at 6 months is 19.60 and mean percentage change after 6 months of treatment is 5.19. The p-value is 0.32 and 0.9 (at 3 and 6 months respectively) which is not significant ($p < 0.05$). Hence there was no significant decline or improvement in HVLTR score from baseline.

DISCUSSION

WBRT followed by boost improves local control compared with WBRT alone. Additionally, it may be advantageous to deliver a radio surgical boost for gross disease simultaneously, rather than sequentially, to reduce tumor cell proliferation and accelerated repopulation as these are the prime causes of treatment failure. The optimal treatment of multiple brain metastases has been the subject of increased controversy in the last decade and is a research question of great epidemiologic impact.

Age

Graf et al. study amongst 230 patients for site preference of metastatic tumors in brain observed that mean age of patients was 61.2 years and most common occurrence in 6th and 7th decade.¹⁵

A retrospective analysis aimed to evaluate clinical dose intensification in patients with brain metastasis (BM's) by Dobi et al. taken a total of 468 patients. The mean age of the population at the time of BM detection was 60.7 years and 6th -7th decade was the most common presenting age group.¹⁶

Table 2: Dosimetric Parameters of Hippocampus in patients of study group

S. No.	<i>Dmax (in Gy) Hippocampus</i>			<i>Dmin (in Gy) Hippocampus</i>			<i>Dmean (in Gy) Hippocampus</i>		
	<i>Right</i>	<i>Left</i>	<i>Combined</i>	<i>Right</i>	<i>Left</i>	<i>Combined</i>	<i>Right</i>	<i>Left</i>	<i>Combined</i>
1	15.87	16.85	16.79	12.98	13.4	13.76	14.55	15.41	14.96
2	16.82	16.94	16.9	10.46	11.3	10.59	13.05	14.35	13.68
3	13.62	15.61	14.27	9	8.47	8.4	10.51	10.18	10.35
4	13.07	13.54	13.37	10.66	10.16	10.17	11.33	11.04	11.15
5	16.14	16.57	16.38	9.88	9.79	9.83	11.75	11.73	11.74
6	14.34	13.87	14.11	9.1	10.09	9.23	10.9	11.3	11.02
7	15.21	12.35	14.39	9.53	9.26	9.31	10.92	10.17	10.56
8	11.68	11.17	11.47	8.6	8.39	8.46	9.55	9.35	9.45
9	13.18	12.82	13.05	8.7	8.65	8.68	9.96	9.81	9.89
10	11.59	11.28	11.42	9.46	8.8	8.9	10	9.57	9.78
11	14.92	13.57	14.17	8.01	7.4	7.49	10	9.53	9.76
12	11.9	16.6	15.3	8.6	12.95	8.7	9.5	22.73	15.93
13	11.93	11.52	11.77	8.29	8.44	8.34	9.39	9.42	9.4
14	15.73	14.08	15.18	9	8.93	9	10.7	10.4	10.6
15	12.97	13.44	13.16	9.47	9.21	9.31	10.58	10.59	10.58
16	12.94	13.66	13.28	8.61	8.42	8.47	10	9.9	9.9
17	12.38	14	13	8.78	8.33	8.41	10	9.84	9.98
18	13.58	12.77	13.12	8.88	8.86	8.87	10	9.88	9.96
19	14.22	13.45	13.71	8.65	8.32	8.36	9.93	9.75	9.82
20	11.71	12.18	11.97	9.22	9.11	9.14	10	9.94	10
21	11	11.38	11.22	9.36	9.08	9.11	9.9	9.77	9.84
22	32.81	32.77	32.8	31.66	31.19	30.67	32.35	31.84	32.16
23	34.63	36.56	31.64	32.15	31.74	29.28	33.4	34.04	30.51
Mean	13.56	13.7	13.72	9.29	9.39	9.16	10.79	11.71	11.26
SD	1.81	2.12	1.84	1.27	1.75	1.5	1.45	2.08	2.08

Gupta et al. in an analysis over survival in 116 patients with brain metastasis, concluded that the commoner age-group for brain metastasis occurrence was the 5th to 7th decade with the median age was 53 years, with 57.7% of patients being more than 50 years of age.¹⁷

Similar results were observed in our study group, with maximum patients of brain metastasis fall in 7th decade (61-70 yrs), mean age of patients with brain metastasis was 55.34 years, median age was 55 yrs and age range was 28 – 77 years. It can be concluded that due to increase awareness among population and advancement of technologies, diagnosis at earlier age is seen.

Sex

Jill S et al. in a population based study over incidence proportions (IP) of brain metastasis patients, IP% was significantly higher for female patients with lung cancer, and significantly higher for male patients with melanoma.¹⁸ Study by Lagerwaard et al. over 1292 patients of brain metastasis for identification of prognostic factors observed male predominance with male: female ratio of 1.68:1.¹⁹

Sun et al. in an interactive view on sex differences in both primary and secondary brain tumors postulate that excluding sex-specific

cancers like breast cancer, males have significantly higher rates of brain metastases than females in almost all cancer types.²⁰

Che et al. in his study on midlife brain metastasis over 2,67,327 patients concluded that middle- aged females were at higher risk of developing brain metastasis than males.²¹

Similar findings of the above study resemble with our study, where brain metastasis more commonly seen in middle- aged females than in males, with Male: Female ratio 1: 1.9. Though some studies data shows males have comparatively high incidence of brain metastasis but there is no specific data to justify this controversy which needs to be explore more.

Primary Diagnosis

A single institutional review study on identification of prognostic factors in patients with brain metastasis done by Lagerwaard et al. ascertained that majority of patients had lung (56%) or breast (16%) as primary disease.¹⁹

Phase II Trial done by Gondi et al. over 113 patients of brain metastasis, to assess neurocognitive functions had Lung (56%) as the most common primary tumor site followed by breast (15%).²²

Table 3: Dosimetric parameters of OAR's (Organ at risk) in patients of study group

S. No.	PRV Brain stem (Dmax)	PRV Spine (Dmax)	Optic Chiasma (Dmax)	Optic nerve (Dmax)		Cochlea (Dmean)		Eye (Dmax)		Lens (Dmax)	
				(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)
1.	33.55	31.2	32.79	31.32	28.73	29.82	30.03	22.88	24.63	8.15	7.33
2.	30.96	28.42	28.72	25.46	25.31	19.04	20.06	19.1	16.26	3.5	3.63
3.	31.75	31.18	31.37	32.2	33.1	30.65	30.68	24.54	29.23	8.39	7.01
4.	31.54	10.2	34.04	11.08	13.02	28.12	29.67	20.55	17.69	6.7	7.98
5.	32.76	1.06	31.12	29.6	32.4	25.03	24.3	27.86	31.6	6	5.9
6.	39.34	26.37	37.65	35.84	34.88	32.33	32.12	30.3	34.13	4.68	6.32
7.	34.39	32.73	34.41	31.72	31.52	29	30.27	30.65	32.56	6.61	7
8.	31.3	30.3	30.65	33.37	28.92	24.43	24.99	22.83	23.25	5.9	6.84
9.	35.31	33.12	35.55	31.48	33.37	28.73	28.41	26.11	26.85	7	5.85
10.	37.36	33.28	34.42	35	33.53	30.23	30.57	35.5	35.32	6.8	7.4
11.	14.88	28.58	34.74	32.26	31.7	27.96	24.66	24.21	27.16	7.6	8.8
12.	47.53	32.77	42.35	35.18	36.32	26.39	30.79	28.65	29.68	5.64	6.46
13.	39	37.59	37.5	30.23	31.94	29.82	29.61	26.65	26.26	6.7	6
14.	35.62	32.6	37.61	29	33.28	26.18	27.37	24.27	34.69	6.1	6.7
15.	32.73	29.68	31.29	31.98	31.07	28.94	29.73	24.6	25.1	6.2	6.18
16.	35.62	32.66	34.75	32.48	31.82	30.15	30.89	28.04	32.86	5.5	6.1
17.	36.4	32.48	35.39	33.84	31.73	30.46	31.27	31.53	23.06	5.91	6.49
18.	37.14	34.51	35.89	32.66	31.56	28.84	30.7	30.85	31.03	6.1	6.2
19.	36.34	29.5	35.56	34.45	30.14	32.58	30.15	23.36	28.19	5.96	6.43
20.	35.49	32.58	34.11	32.6	26.59	30	30.51	23.67	19.88	6.45	4.53
21.	33.89	32.32	33.68	36.54	34.46	24.38	24.59	27.9	24.75	9.11	7.01
22.	33.25	33.3	30.28	29.97	30.21	28.89	30.34	27.37	26.69	6.16	6.63
23.	38.46	30.64	36.86	38.84	26.32	22.14	22.93	18.94	19.32	7.53	7.57
Mean	35.54	29.43	34.38	30.51	31.61	28.46	28	26.10	26.96	6.46	6.53
SD	5.59	7.97	3.03	4.69	5.28	3.22	3.24	4.12	5.44	1.19	1.05

A retrospective study by Dobi et al. on boost irradiation along with whole brain radiotherapy in patients of brain metastasis, the commonest primary neoplasm was that of the lung in 68.9% (16% of the latter was small cell lung cancer without prior prophylactic skull irradiation), followed by breast in 7.9%.¹⁶

In a study by Zhong J. et al. on outcomes of whole brain radiation with simultaneous in-field boost (SIB), the most common primary tumor types were non-small cell lung cancer (31%) and breast cancer (31%).²³

Gupta et al. study over survival analysis in 116 patients with brain metastasis study concluded that lung cancer was the most common primary malignancy 80 (68.9%) followed by breast cancer 23 (19.8%).¹⁷

Similar results resemble in our study also with brain metastasis more commonly seen in cancer lung (43.47%) followed by cancer breast (26.08%). There are many theories which support cancer lung as leading cause of brain metastasis like correlation of

non-small cell lung cancers with EGFR but still specific reason is debatable and to be explored further. Since, incidence of cancer lung is highest and also it is the leading cancer type in the world and 4th most common cancer in India in both sexes according to GLOBOCON 2022 data, which further signifies its increased tumor burden in the population. Its presenting symptoms also mimics a lot with other lung diseases, which delays its diagnosis and further increases its chances to be presentable in late stages, thus increases risk of brain metastasis, could be another reason to be explored.

Clinical Features

Lagerwaard et al. in his study on prognostic factors in patient with brain metastasis over 1292 patients, found out that headache (53%) was the most common presenting symptom followed by motor weakness (38%), cerebellar dysfunction (26%), seizures (22%), and dysphasia (14%).¹⁹

Table 4: Neurocognitive Function Evaluation (Mini Mental State Examination)

Hippocampal sparing	Pt. No.	Mini Mental State Examination (MMSE)					
		Before Radiotherapy (0 month)		After Radiotherapy (3 months)		After Radiotherapy (6 months)	
		Score	Category	Score	Category	Score	Category
Achieved	1	20	Mild	21	Mild	22	Mild
	2	19	Mild	20	Mild	20	Mild
	3	20	Mild	21	Mild	22	Mild
	4	19	Mild	19	Mild	21	Mild
	5	22	Mild	23	Mild	22	Mild
	6	30	Normal	27	Normal	27	Normal
	7	28	Normal	26	Normal	27	Normal
	8	18	Mild	19	Mild	19	Mild
	9	20	Mild	21	Mild	22	Mild
	10	19	Mild	21	Mild	22	Mild
	11	15	Severe	17	Severe	16	Severe
	12	23	Mild	24	Normal	24	Normal
	13	23	Mild	25	Normal	26	Normal
	14	19	Mild	21	Mild	20	Mild
	15	21	Mild	23	Mild	22	Mild
	16	19	Mild	20	Mild	19	Mild
	17	19	Mild	19	Mild	21	Mild
	18	23	Mild	25	Normal	26	Normal
	19	22	Mild	24	Normal	25	Normal
	20	26	Normal	25	Normal	26	Normal
	21	28	Normal	26	Normal	25	Normal
Not Achieved	22	17	Severe	16	Severe	16	Severe
	23	30	Normal	28	Normal	26	Normal
Mean		21.73		22.21		22.43	
Std. dev		4.12		3.23		3.24	
P-value	0.66				0.52		

In a study by Saha et al. over clinical profile and demographics done on 72 patients with brain metastasis, Headache (66.7%) was the most common presenting symptom followed by vomiting (54.16%), neurological deficit (36.11%) and seizure (25%).²⁴

In our study, it was found that majority of the patients had headache (73.91%) as most common presenting symptom followed by vomiting (21.73%). Other features observed were motor weakness (21.73%), seizure episodes (17.39%) and visual symptoms (8.69%), which correlates with the above studies. The most possible mechanism for the above symptoms must be due to traction and resultant displacement effect on the blood vessels draining into sinuses and direct pressure effect by tumor on cranial nerves.

Tumor Site

Gupta et al. study on prognostic factors in brain metastasis patients affecting survival observed that, in 51.7% patients' multiple lobes of brain were involved.¹⁷

In another study by Saha et al. done on 72 brain metastasis patients, supratentorial involvement (97.2%) was much commoner

than infratentorial involvement (2.8%) and of which parietal lobe was the commonest site of involvement constituting 48% of all lesions.²⁴

Similar findings observed in our study, with brain metastasis more commonly located in Supratentorial region (60.86%) than infratentorial region (8.69%) and of which frontal lobe was the commonest site of involvement constituting 39.13% of all lesions, followed by fronto-parietal lobe (17.39%), and further cerebellar region (13.04%).

Number of Lesions

Dobi et al. in a retrospective study observed that in the case of low number of the BM (1–3) and in the case of multiple (>4) metastases, the OS difference between the 30Gy and escalated groups were significant. ($p = 0.002$ and 0.001 respectively).¹⁶

In a retrospective study by Shirasawa M. et al. on prognosis of oligometastatic and polymetastatic lesions in 141 patients of brain metastasis concluded that the prognosis of patients with Extensive disease-small cell lung carcinoma (ED-SCLC) with oligometastasis were significantly superior to those of patients with polymetastasis

Table 5: Neurocognitive Function Evaluation (Hopkins Verbal Learning Test-Revised Score)

Hippocampal sparing	Pt. No.	Hopkins Verbal Learning Test Revised (HVLTR)			
		Before Radiotherapy (0 month)	After Radiotherapy (3 months)	After Radiotherapy (6 months)	% change
Achieved	1	14	12	11	-8.33
	2	15	14	16	+2.78
	3	22	20	24	+5.55
	4	16	16	18	+5.56
	5	18	17	16	-5.56
	6	27	24	23	-11.11
	7	12	12	16	+11.11
	8	18	18	20	+5.55
	9	17	15	19	+5.55
	10	17	16	16	-2.77
	11	17	17	16	-2.77
	12	20	18	21	+2.78
	13	21	18	19	-5.55
	14	19	18	22	+8.34
	15	18	17	20	+5.55
	16	22	21	24	+5.55
	17	25	22	21	-11.11
	18	19	17	18	-2.77
	19	24	26	24	0
	20	26	24	25	-2.77
	21	22	20	22	0
Not achieved	22	18	21	20	+5.55
	23	21	20	20	-2.78
Mean		19.47	18.39	19.60	5.19
Std. Dev		3.81	3.61	3.43	3.16
P-value		0.32		0.9	

[16.0 (95% CI, 11.0–21.0) months vs. 6.9 (95% CI, 6.0–7.8) months; $p < 0.001$]. Patients with ED-SCLC and oligometastasis may have improved survival than those with polymetastasis.²⁵

In our study, it was found that majority of the patients had oligometastasis (91.3%) and also in those majority had single brain metastasis (56.52%) and number of lesions ranges from 1 to 10 but there is no additional survival benefit observed in our study group.

PTV and Hippocampal dosimetric parameters

Neurocognitive toxicity represents a spectrum of different toxicities, and the time course of these can vary significantly. Most authors have generally focused on severe dementia and described this as a "late toxicity," occurring several months to years following cranial irradiation.

De Angelis et al. suggested that as many as 11% of long-term brain metastases survivors (>12 months) treated with cranial irradiation develop severe dementia, but only with the use of larger dose-per-fraction schedules. This provides the rationale to explore the clinical feasibility of hippocampal sparing during WBRT.²⁶

In a prospective study by Hsu et al. on brain metastasis patients to assess hippocampal avoidance in whole brain radiotherapy using VMAT, had mean values for the brain metastases were as follows: conformity number = 0.73 ± 0.10 , target coverage = 0.98 ± 0.01 and homogeneity index = 0.07 ± 0.02 . For the whole brain, the mean target coverage and homogeneity index were 0.960 ± 0.002 and 0.39 ± 0.06 , respectively. The mean hippocampal dose was 5.23 ± 0.39 Gy.²

A study by Gondi et al. on hippocampal sparing during whole brain radiotherapy by LINAC based IMRT technique on brain metastasis patients with prescription dose of 30Gy in 10 fractions, the median dose of hippocampus (both combined) was 7.8Gy and maximum dose of 15.3Gy.²⁷

Levra G. et al. in a dosimetric study to assess feasibility of hippocampus avoidance in whole brain radiotherapy (WBRT) with simultaneous integrated boost (SIB) over 10 patients with brain metastasis had mean HI was 0.083 ± 0.03 (range, 0.03–0.16), mean CI of 0.78 ± 0.17 (range, 0.41–0.98). Hippocampal mean dose was 7.7 ± 0.3 Gy (range, 7.4–8.5 Gy), mean Dmax dose

10.5 ± 0.5 Gy (range, 9.4–11.3 Gy), mean D100% dose 6.7 ± 0.3 Gy (range, 6.3–7.3 Gy) and also concluded that WBRT plus SIB with Hippocampal avoidance was feasible with advancement of technology like VMAT.²⁸

In our study hippocampus sparing was done by VMAT and IMRT planning techniques with the mean Conformity index was 1.28 ± 0.34 and homogeneity index was 0.063 ± 0.02 showing feasibility and good hippocampal avoidance, resembling with the above studies.

A study by Popp et al. with the aim of investigating feasibility of hippocampal sparing while WBRT+SIB for multiple brain metastasis in 124 patients, the mean dose to the bilateral hippocampi was 6.8 ± 0.5 Gy (median, 6.7 Gy; EQD2 / α = 2), whereas the dose to 40% of the hippocampal volume (D40%) was on average 6.7 ± 0.5 Gy (median, 6.6 Gy; EQD2 / α = 2). The average D2% to the hippocampus was 11.2 ± 1.9 Gy (median, 10.3 Gy; EQD2 / α = 2), and D98% was 5.4 ± 0.3 Gy (median, 5.4 Gy; EQD2 / α = 2).²⁹

Zhong J. et al. in a prospective study on outcomes of whole brain radiation (WBRT) with simultaneous in-field boost (SIB) for treatment of brain metastasis taken 13 patients, dose to the hippocampus was not specifically constrained, the median mean dose (Dmean) and maximum point dose (Dmax) were 26.8 Gy (range: 26.1–41.3 Gy) and 28.6 Gy (range: 25.2–49.8 Gy), respectively.²³

A multicentric trial by Grosu et al. comparing impact of hippocampal avoidance (HA) on neurocognitive functions after HA-WBRT+SIB v/s WBRT+SIB done on 132 patients with multiple brain metastasis, with prescribed dose of 51Gy in 12 fractions in HA-WBRT+SIB arm, had mean dose in the bilateral hippocampus of under 10 Gy (EQD2 / α = 2 of 7.1 Gy).³⁰

In a Phase II Trial of Hippocampal-Sparing Whole Brain Irradiation with Simultaneous Integrated Boost (HSIB-WBRT) for Metastatic Cancer done by Westover et al. enrolled 49 patients, the mean dose, minimum dose, and maximum dose achieved for the hippocampus were 13.2 Gy (± 1.3), 11.5 Gy (± 1.5), and 15.8 Gy (± 1.5) Gy, respectively.³¹

In a study by Grosu and Popp et al. with the aim of hippocampal sparing during whole brain radiotherapy in 30 patients with brain metastasis, the prescribed dose was 30Gy in 12 fractions to whole brain and 36–51Gy in 12 fractions SIB for brain metastasis, the mean dose to the hippocampus was 10.07 ± 0.96 Gy with conventional planning and 8.79 ± 0.99 Gy with hippocampal blocking (p < 0.0001). D98% was on average 8.49 ± 0.50 Gy with conventional planning and 7.87 ± 0.28 Gy with hippocampal blocking (p < 0.0001), while D2% was 14.48 ± 3.38 Gy and 10.88 ± 3.48 Gy respectively (p < 0.0001). All in all, the mean hippocampal dose could be reduced by 1.28 ± 0.64 Gy through hippocampal blocking.³²

Perlow et al. in a phase II trial to preserve neurocognitive function in patients treated for brain metastases, memory avoidance structures had a median dose range of 10.8–14.2 Gy and a maximum dose range of 15.6–22.7 Gy. The mean dose to the memory avoidance structures was 12.7 Gy (range, 11.5–13.8 Gy).³³

Similar dosimetric findings observed in our study, where the dosimetric parameters of hippocampus (both combined) had mean Dmax 13.72 ± 1.84 Gy (11.22 – 16.9), Dmin 9.16 ± 1.5 Gy (8.34 – 13.76), Dmean 11.26 ± 2.08 Gy (9.4 – 15.93) in 21 patients where hippocampal sparing was achieved. The 2 patients where Hippocampus sparing was not achieved, the dosimetric parameters were Dmax 32.22 ± 0.82 Gy (31.6–32.8), Dmin 29.98 ± 0.98 Gy (29.28–30.67), Dmean 31.34 ± 1.16 Gy (30.51–32.16).

In those patients where hippocampus sparing was achieved,

either the no. of lesions was ≤ 4 or PTV was not in close proximity of the hippocampus. In those 2 patients where hippocampus sparing was not achieved, 1 patient had 10 lesions and other patient had 5 lesions and hippocampus was also in close proximity with PTV.

Neurocognitive Functions

In a Multi-Institutional Phase II Trial done by Gondi et al. over 113 patients of brain metastasis, to assess the role of hippocampal neural stem-cell injury and neurocognitive functions during whole brain radiotherapy with hippocampal avoidance showed that mean relative decline in HVLt-R DR from baseline to 4 months was 7.0% (95% CI, -4.7% to 18.7%), significantly lower in comparison with the historical control (P < .001). No decline in QOL scores was observed, which is similar to our study in which we saw that there is no significant decline in neurocognitive functions.²²

Tsai et al. in his study to demonstrate the impact of delivering HA-WBRT on NCF changes in 40 patients receiving WBRT found no statistically significant differences were found between various NCF scores obtained at baseline and 4 months post-radiotherapy and also support the fact that conformal hippocampal sparing during WBRT might preserve patients neurocognitive functions.³⁴

Zanirato et al. in a systematic literature review, concluded that there are no significant changes in NCF (i.e., verbal and nonverbal learning memory, executive functions, and psychomotor speed) between baseline and 4-month follow-up after RT and only a mean relative decline in delayed recall at 4 months (7% compared to 30% of historical control).³⁵

In a Phase II Trial of Hippocampal-Sparing Whole Brain Irradiation with Simultaneous Integrated Boost (HSIB-WBRT) for Metastatic Cancer done by Westover et al. mean decline in Hopkins Verbal Learning Test-Revised delayed recall (HVLt-R DR) at 3 months after HSIB-WBRT was only 10.6% (95% CI, -36.5% to 15.3%). Also concluded that HVLt-R DR after HSIB-WBRT was significantly improved as compared to historical outcomes in patients treated with traditional WBRT, while achieving intracranial radiosurgery (SRS). This technique can be considered in select patients with multiple brain metastasis who cannot otherwise receive SRS.³¹

HVLt scores in our study also resemble with above study as there is no significant decline in HVLt-R scores on assessment after 3 and 6 months of completion of radiotherapy (p-value is 0.32 and 0.9 at 3 and 6 months respectively which is not significant (p < 0.05).

Study by Buhai Wang et al. on neurocognitive function assessment while sparing hippocampus during whole brain radiotherapy in non-small cell lung cancer patients with brain metastasis concluded that HA-WBRT might have a protective effect on long-term neurocognitive function (NCF) and no significant change in neurocognitive functions in short term.³⁶

Similar results were observed in our study, the mean value of Mini Mental Score Examination (MMSE) before radiotherapy (0 month) was 21.73, after radiotherapy at 3 months was 22.21, and at 6 months was 22.43. There was MILD neurocognitive deficit noted. The p-value is 0.66 and 0.52 (at 3 and 6 months respectively) which is not significant (p < 0.05). Out of 23 study patients, Hippocampal sparing was achieved in 21 patients. The baseline neurocognitive impairment was mild in 16 patients, severe in 1 patient and rest 4 were normal. The degree of impairment has no change in 17 patients and improved to normal from mild category in 4 patients after 3 months of follow-up and remains same even after 6 months of follow up.

The 2 patients where Hippocampus sparing was not achieved,

there was no change in neurocognitive functions after 3 and 6 month of follow-up.

Conclusion

Neurocognitive impairment is of concern in the setting of WBRT-SIB delivered for Brain metastasis. Promising results from our study demonstrated that HA-WBRT-SIB might have a protective effect on long-term neurocognitive function. Thus, HS-WBRT+SIB can be an efficient therapeutic option for patients with brain metastasis to spare neurocognitive functions to a great extent and is also associated with improved local tumor control of existing metastasis. This may probably lead to better intracranial progression free survival, reduction in neurological death rate, and an acceptable risk of radiation necrosis.

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