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Neurocognitive function assessment for cancer patients with brain metastases following whole brain radiation therapy: a single institutional observational study from a tertiary care hospital

Rahi Das[1], Amitabha Chakrabarti[*2]

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1. MBBS, Junior Resident
Department of Radiotherapy, R. G. Kar Medical College & Hospital, Kolkata - 700004, West Bengal, India
Email: rahi.das1995@gmail.com

2. MBBS, MD (Radiotherapy), Associate Professor and Corresponding Author
Department of Radiotherapy, R. G. Kar Medical College & Hospital, Kolkata - 700004, West Bengal, India
Address: Emami City, A,603-6 2 Jessore Road, Dumdum, Kolkata700028-, West Bengal, India.
Telephone No: + 91 8902108146
Email: amic4102@gmail.com

ABSTRACT

Background: Whole Brain Radiation Therapy (WBRT) has been effective in the management of brain metastases, giving good local control but has shown to have potential neurocognitive effects. Assessing its effect on neurocognitive function is decisive assessing quality of life and therapeutic decision-making.

Methods: This is an observational study at R. G. Kar Medical College and Hospital from May 2022 to April 2023 involving 60 biopsy-proven carcinoma patients with brain metastases fulfilling inclusion and exclusion criteria. All received 30Gray (Gy)/10# WBRT over 2 weeks. Neurocognitive function assessments using Mini-Mental State Examination (MMSE) were conducted before and at the 2nd, 3rd, and 6th months post-WBRT.

Results: The study, encompassing a median age of 58, revealed that 43.3% had lung primary and 35% breast primary. The mean MMSE score was 27 pre-radiation. Following WBRT, a more than equal to 3-point MMSE decrease occurred in 6.6%, 11.6%, and 18.3% at the 2nd, 3rd, and 6th months post-radiation respectively. Neurocognitive decline was 36% for those above 50 years and 64% for those below 50 years by the 6th month. In 2nd month 88.3% of patients had controlled disease having a decrease in MMSE score by 1.6, while 11.6% with uncontrolled disease showed 3.1 MMSE change and the same trend continued in 3rd and 6th month observations.

Conclusion: WBRT is crucial for local control of brain metastases, but neurocognitive decline, especially under 50, is of major concern. Study results offer awareness for pre-treatment counseling on WBRT benefits, risks, and consideration for Hippocampal Avoidance of WBRT or WBRT with memantine, and requires further extensive research.

Keywords: Cranial Irradiation, Brain Neoplasms, Radiotherapy, Cognition.

INTRODUCTION:

Brain metastases are a frequent aftermath of cancer, affecting about 24–45% of cancer patients.[1] Whole Brain Radiation Therapy (WBRT) is considered the gold standard in the treatment of brain metastases.[2] It gives good local control but also has potential neurocognitive effects. The cognitive consequences of whole brain radiation therapy (WBRT) pose a significant concern, leading to fear among physicians about administering this treatment to patients with brain metastases (BM) following the availability of treatments like stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT). [3] This delay in decision-making is problematic in patients with controlled or no extra-cranial disease and with primary tumors that are radiosensitive. In such cases, the goal of treating newly diagnosed BM is not only not palliation but also to control brain metastases, demanding an aggressive approach.

WBRT is associated with several concerns as stated below:

- Decline in cognitive function: Patients may experience memory loss, impairment of executive function, and learning and attention issues. These may impair day-to-day life activities and inability to maintain independence. Cognitive decline may not become evident until months after irradiation.[23]
- Quality of Life: The neurocognitive decline may interfere with the patient's simple daily activities, leading to a reduction in the ability to work, socialize and also in maintaining personal relationships.
- Radiation can affect the hypothalamic-pituitary axis, leading to hormonal imbalances and may lead to deficiencies that would require lifelong hormone replacement therapy.[24]
- There are potential risk of hearing loss or vision changes attributable to the proximity of the irradiation area to the eyes and ears.[25]
- WBRT can cause radiation necrosis, where brain tissue becomes necrotic because of radiation exposure. This condition can imitate tumor recurrence and present with symptoms like headaches, seizures, and focal neurological deficits.[26]
- Acute Effects: 1) Many patients experience remarkable fatigue during and after treatment, which can last for weeks or months.

2) Loss of scalp hair: Although temporary, hair loss may be distressing for patients and affect their self-confidence.[27]

3) Dermatitis may be caused in the scalp area, leading to itching, redness, and discomfort.

- Long-Term Risks: 1) Secondary Malignancies: Rare but there is a risk of developing secondary cancers because of radiation exposure, particularly in younger patients.[28]

2) Leukoencephalopathy: Long-term exposure to radiation may result in leukoencephalopathy which is a white matter brain disease that can aggravate cognitive decline and other neurological symptoms.[29]

Neurocognitive function (NCF) is an indicator of both brain tumours volume and the detrimental effect of radiation to brain.[4] Assessment of the impact of whole-brain radiation therapy (WBRT) on NCF is crucial for making individual patient's treatment decisions. However, there is a scarcity of broad data on neurocognitive function impairment following WBRT. Also, the reported rates of NCF decline following WBRT varies significantly across studies. [5,6] To guide therapeutic decision making, understanding the impact of WBRT on neurocognitive function (NCF) is critical. There are few previous studies showing effect of neurocognitive function following WBRT but very scarce data is available on populations of Eastern India.

METHODS AND MATERIALS:

This is an Observational Single Institutional Study, conducted at the Radiotherapy Department of R. G. Kar Medical College and Hospital, Kolkata from May 2022 to April 2023. The study includes patients with brain parenchymal metastases in patients of biopsy proven cancer of solid tumours meeting the inclusion and exclusion criteria.

Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2, more than 3

brain metastases, those willing to give consent for the study and patients who refused surgery were included while patients with ECOG PS > 2, patient with known psychiatric illness that can cause neurocognitive decline, patients with expected survival of less than 1 year and prior radiation in brain were excluded from the study. Factors often associated with improved survival in brain metastases patients:

- Patients with better performance status (ECOG PS 0,1,2 were included in the study)
- The number and size of brain metastases can impact survival. Patients with fewer and smaller metastases may have a better prognosis
- Patients with fewer comorbidities and better overall general health conditions tend to tolerate treatment better and may have improved survival. (Patients with known co-morbidities were excluded from the study)
- Prognostic tools, such as the Graded Prognostic Assessment (GPA) or Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) can help clinicians estimate survival probabilities based on multiple factors.

Sixty patients were included in the study and all received WBRT with a dose of 30Gy in 10#, 5 days a week, over 2 weeks with a Linear Accelerator (LINAC) machine and followed up to 6 months of WBRT. Neurocognitive function assessment was done with Mini-Mental State Examination (MMSE) scoring and response was assessed by Contrast-Enhanced Magnetic Resonance Imaging (CEMRI) at 2nd, 3rd, and 6th month following radiation. Statistically meaningful change in neurocognitive function was defined as a three-point (≥3) change in the MMSE score.[7]

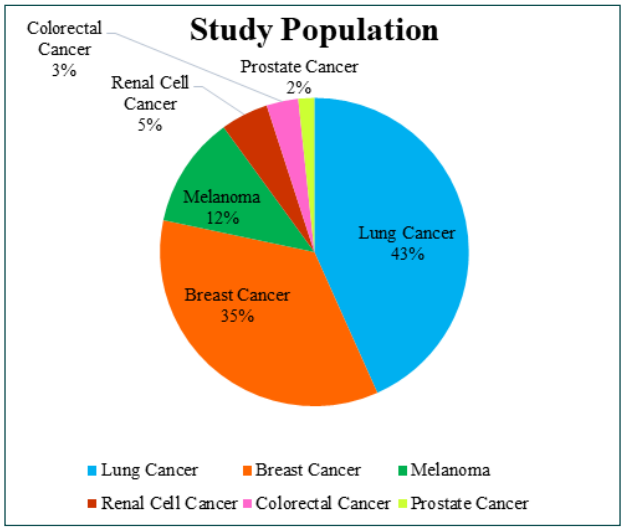
All study patients underwent CT simulation with the Siemens Somatom Definition AS 20-slice flat couch CT simulator. The delineation of target volumes and organs at risk (OARs) was done, and 3D CRT treatment planning with the Eclipse version 15.1 treatment planning system was done. Treatment involved the use of 6 MV external beam photon energy, employing 3D conformal radiotherapy (3D-CRT) techniques on the Varian TrueBeam version 2.7 Linear Accelerator machine. Data were summarized using Microsoft Excel, and Online Statistics Calculator-DATAtab and SPSS software (version 21) were used for statistical analysis. Two faculty members with two medical physicists were involved in the whole planning and delivery process.

RESULTS:

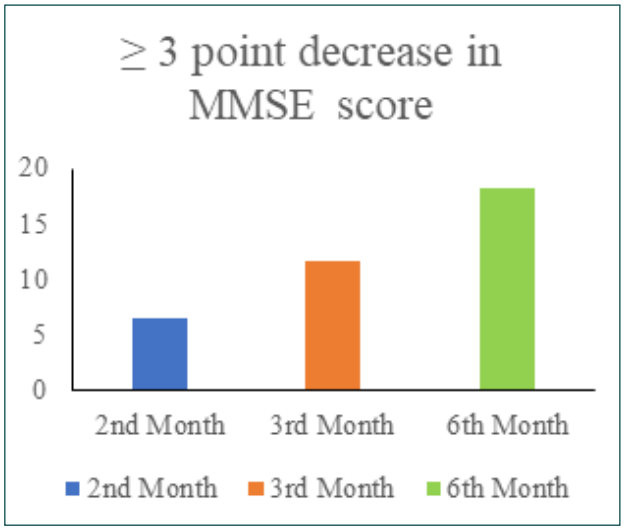
- The median age of the study population was 58 years and the gender distribution was 65% male and 35% female. 43.3% of the patients were from lung primary and 35% from breast primary and the rest from others.
- Mean MMSE score of the study population was 26.93 +/- 1.94 before start of radiation.
- We found a≥ 3-point decrease in MMSE score in 6.6% of patients in 2nd month,11.6% in 3rd month, and 18.3% in

Table 1. Demographics, Tumour site and Number of Brain metastases, Time from first diagnosis of cancer, History of steroid consumption, Status of extra cranial disease , GPA (Graded Prognostic Assessment) Score

Age	**Median: 58 years, Minimum: 30 years, Maximum: 73 years**
Gender	**Male: 39 (65%), Female: 21 (35%)**
Primary Site	**Lung: 26 (43.3%), Breast: 21 (35%), Melanoma 7 (11.67%), Renal Cell Cancer 3 (5%), Colorectal Cancer 2 (3.33%), Prostate Cancer 1 (1.67%)**
No. Of Mets	**Four: 32 (53.3%), Five: 19 (31.67%), Six: 9 (15%)**
No. Of lesions	**<5 (32 patients i.e. 53.3%), 5-10 (28 patients i.e. 46.67%), >10 (0 patients)**
Time from first diagnosis of cancer	**7 +/- 2.65 months**
History of steroid consumption	**Present (93.33%); Absent (6.67%)**
Status of extra cranial disease	**Controlled (80%); Uncontrolled (20%)**
GPA (Graded Prognostic Assessment) Score	**3.52 +/- 0.398 (Range: 3.0 to 4.0)**
Timing of their systemic disease	**7 +/- 2.65 months**



Graph 1. Study Population

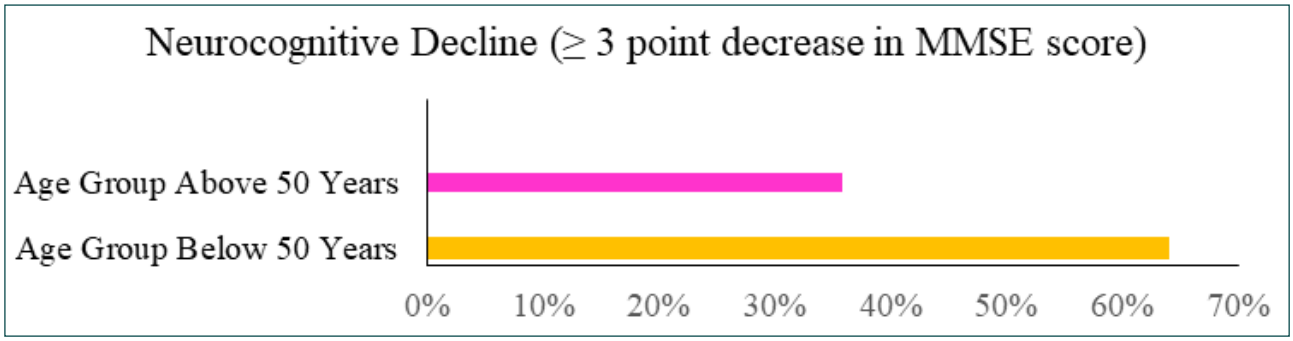


Graph 2. Statistically significant Neurocognitive Function decline by the end of 2nd, 3rd and 6th month post WBRT

the 6th month following WBRT from the baseline value.

- Neurocognitive function decline was 36% among patients above 50 years of age and 64% among patients below 50 years of age by the end of 6th month. (P value 0.00007)
- Patients whose radiographic imaging displayed complete resolution, improvement, or unchanged brain metastases were labelled as having controlled disease. While individuals with deterioration of brain metastases in imaging were classified as having uncontrolled disease [8].
- At 2nd Month:
  - 88.3% of the patients showed controlled disease with a mean change of MMSE score of 1.6 +/- 0.85
  - 11.6% of the patients showed uncontrolled disease with a mean change of MMSE score of 3.1 +/- 0.64
- At 3rd Month:
  - 85% of the patients showed controlled disease with a mean change of MMSE score of 1.5 +/- 0.92
  - 15% of the patients showed uncontrolled disease with a mean change of MMSE score of 4.2 +/- 1.7
- At 6th Month:
  - 72.2% of the surviving patients showed controlled disease with a mean change of MMSE score of 2.5 +/- 0.36
  - 27.78% of the surviving patients showed uncontrolled disease with a mean change of MMSE score of 5.4 +/- 1.31

* Only 54 (90%) patients survived at 6th month.



Graph 3. Study Neurocognitive Function decline above and below 50 years

Table 2. Controlled/Uncontrolled Brain Metastases and Average change of MMSE Score by 2nd Month following WBRT

AT 2nd MONTH		
BRAIN METS	**% OF PATIENTS**	**AVG. CHANGE IN MMSE SCORE (with Standard Deviation)**
Controlled	88.3	1.6 +/- 0.85
Uncontrolled	11.6	3.1 +/- 0.64

Table 3. Controlled/Uncontrolled Brain Metastases and Average change of MMSE Score by 3rd Month following WBRT

AT 3rd MONTH		
BRAIN METS	**% OF PATIENTS**	**AVG. CHANGE IN MMSE SCORE (with Standard Deviation)**
Controlled	85	1.5 +/- 0.92
Uncontrolled	15	4.2 +/- 1.7

Table 4. Controlled/Uncontrolled Brain Metastases and Average change of MMSE Score by 6th Month following WBRT

AT 6th MONTH		
BRAIN METS	**% OF SURVIVING PATIENTS**	**AVG. CHANGE IN MMSE SCORE (with Standard Deviation)**
Controlled	72.2	2.5 +/- 0.36
Uncontrolled	27.78	5.4 +/- 1.31

DISCUSSION:

The common primary cancers that spread to the brain include lung cancer, breast cancer, renal cancer, melanoma, and colorectal cancer. About 6% of individuals diagnosed with these primary carcinomas develop brain metastases within the initial year of cancer diagnosis.[9] The failure of medical treatments for brain metastases (BM) is widely recognized, primarily due to the challenge of penetration of the blood-brain barrier. WBRT promises good local control in brain metastasis.

Radiation-induced neurocognitive function impairment follows a biphasic pattern: an initial transient subacute decline with a peak at 4 months following late delayed irreversible impairment of neurocognitive function (NCF) several months or years after completion of whole brain radiation therapy (WBRT). [10-13] The goal of this study was to appreciate the decline in neurocognition following WBRT for therapeutic decision-making.

Neurocognitive function (NCF), evaluated by MMSE scores, shows impairment with a notable association with uncontrolled brain metastases. Unfortunately, subsequent studies were not available, except for the study by Aoyama et al., which indicated a persistent decline in neurocognitive function over time. [14,15] Their findings published that there was a lower risk of brain tumor recurrence in patients with solitary brain metastases (BM) in the absence of extracranial metastases contrary to those with multiple BMs or extracranial disease. As a result, they proposed delaying of WBRT in those cases, as the risk of brain tumor recurrence was 31% at 6 and 12 months in low-risk patients without upfront WBRT, allowing 69% of patients to avoid dispensable treatment.

In our study, the study population had a median age of 58 years, with a notable representation of patients from lung primary (43.3%) followed by breast cancer (35%). The mean MMSE score before the start of radiotherapy was 26.93 +/- 1.94. Throughout the study period, it was observed that there are significant trends in neurocognitive function changes following whole

brain radiotherapy (WBRT).

A gradual decline was noted in MMSE scores, with a ≥ 3-point decrease in 6.6% of patients by the 2nd month, 11.6% by the 3rd month, and 18.3% by the 6th month, compared to the baseline values. Stratifying the data by age, it was found that by the end of the 6th month, there was a statistically significant decline in neurocognitive function was 36% in patients above 50 years and 64% in patients below 50 years. Assessing the relation between disease control and MMSE scores, it was observed that in the 2nd month, 88.3% of patients showed controlled disease with a mean MMSE score change of 1.6 +/- 0.85, while 11.6% of patients showed uncontrolled disease with a mean MMSE score change of 3.1 +/- 0.64. This trend continued in the 3rd month (85% controlled, mean MMSE change of 1.5 +/- 0.92; 15% uncontrolled, mean MMSE change of 4.2 +/- 1.7) and the 6th month (72.2% controlled, mean MMSE change of 2.5 +/- 0.36; 27.78% uncontrolled, mean MMSE change of 5.4 +/- 1.31).

The results of our study align with Aoyama (2011), wherein significant neurocognitive deterioration was reported in breast cancer patients post WBRT, though the decline rates in our study appear slightly lower, as Aoyama found a noteworthy cognitive decline in approximately 20% of patients within a similar timeframe.[14] A study by Abe and Aoyama (2012) also noted cognitive declines but prioritized variability based on patient demographics and disease control, noting a 15-25% neurocognitive function decline within 3 to 6 months post-WBRT.[15] Compared to our findings, both these studies highlighted similar trends of neurocognitive decline, with our study showing a bit lower but still significant percentage of affected patients, underlining the greater decline in younger patients (<50 years of age) and those with uncontrolled disease.

These findings suggest a meticulous relationship between disease control and neurocognitive function outcomes, stressing the need for a thorough understanding of both factors in the management of patients undergoing WBRT. Further exploration of these associations might furnish more personalized and effective treatment strategies for patients with brain metastases.

The neurocognitive toxicity due to WBRT must be carefully weighed against the likely neurocognitive decline that may be due to brain disease recurrence. Previous studies have shown a correlation between brain failure, neurocognitive decline, and subsequent alterations in quality of life (QOL).[16-21] Findings from prospective clinical trials have successfully shown the benefit of WBRT, characterized by intracranial control of disease in preserving NCF.[19,22] Especially, these trials highlight that patients with a positive radiologic response to WBRT showed amelioration in executive function and fine motor coordination, although not in memory, suggesting a distinct impairment of hippocampus-related functions by WBRT, leading to the concept of Hippocampus Avoidance WBRT (HA-WBRT).

CONCLUSIONS:

There are concerns regarding impairment of neurocognitive function following whole-brain radiation therapy (WBRT). The maximum control of brain metastases is achievable through WBRT. Hence, it is crucial to minimize the delayed side effects of WBRT. Deterioration of neurocognitive function after nonhippocampal sparing WBRT is a major concern below the age of 50 years. It is essential to develop multiple strategies to prevent and reduce both acute and late toxicities. The outcomes of this study will allow physicians to educate the patients about the importance and drawbacks of this treatment, for pretreatment counseling of the patients about the risks and benefits associated and consideration of Hippocampal Avoidance WBRT (HA-WBRT) or WBRT with memantine and call for a further large study.

LIMITATIONS:

1. As this is a single institutional study, it limits the generalizability of its findings.
2. The study's robustness and its application to a wider

population are compromised due to the relatively small number of participants.

3. Institutional biases may influence the results, considering the study's limitation to a single medical facility.

DECLARATIONS:

1. Funding: No funding was used to support this study.

2. Disclosure: The authors report no conflict of interest in this work.

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