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EVALUATION OF EFFECT ON REMOTE & RECENT MEMORY FUNCTION BY WHOLE BRAIN RADIOTHERAPY WITH TEMOZOLOMIDE GIVEN IN SHORT VERSUS LONG COURSE

Radiotherapy

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ABSTRACT

Introduction: Most common intracranial tumor in adults is brain metastasis. Different fractionation schedules used for whole brain radiation therapy are 20gray/5Fr, 30gray/10Fr, and 40gray/20Fr, which in four weeks have shown equivalent response rate, period of improvement, palliative effect, time to disease progression, and survival. However, there is lacking literature on the effect of different fractionation schedules of radiation therapy on memory function. **Objectives:** Hence, we evaluated memory function in two different fractionation schedules of whole brain radiation therapy (WBRT) inpatients with brain metastases. **Methods:** A total of 50 patients, who were histologically proven primary and recently diagnosed brain metastases, and satisfying eligibility criteria were taken into this study. Patients were randomly assigned to whole brain radiation therapy of 40gray in 20 fractions (group A) and 30gray in 10 fractions (group B) with concurrent Temozolomide. Memory function assessment was done using P.G.I. Memory scale before, during, and after the treatment. **Data Analysis And Results:** Patients in-group A showed improvement in both domains of memory function (Remote and Recent memory) during radiation therapy, compared to group B patients. **Discussion & Conclusion:** Forty Gray in 20 fractions given over four weeks with concurrent TMZ 75 mg/m2 is a better and preferable treatmentoptionforpatientswithbrainmetastasiswithrespecttomemoryfunction.

KEYWORDS

Whole brain Radiotherapy (WBRT), Brain Metastases, Memory Function

1. INTRODUCTION

Five primary tumors account for 80% of brain metastases [2]:

a. Lung Cancer
b. Renal Cell Carcinoma
c. Breast Cancer
d. Melanoma
e. Gastrointestinal Tract Adenocarcinomas (the majority are colorectal carcinoma)

Whole brain radiotherapy (WBRT) is a mainstay of treatment in patients with both identifiable brain metastases and prophylaxis for microscopic disease. The use of WBRT has decreased somewhat in recent years due to both advances in radiation technology, allowing for a more localized delivery of radiation, and growing concerns regarding the late toxicity profile associated with WBRT. This has prompted the development of several recent and ongoing prospective studies designed to provide Level I evidence to guide optimal treatment approaches for patients with intracranial metastases.

In addition to defining the role of WBRT in patients with brain metastases, identifying methods to improve WBRT is an active area of investigation, and can be classified into two general categories: Those designed to decrease the morbidity of WBRT, primarily by reducing late toxicity, and those designed to improve the efficacy of WBRT. Both of these areas of research show diversity and promise, and it seems feasible that in the near future, the efficacy/toxicity ratio may be improved, allowing for a more diverse clinical application of WBRT.

2. Objectives

However, there is no study clearly showing the decline in memory function in brain metastases patients undergoing WBRT treatment. Hence, in this study we evaluated memory function outcomes in patients receiving WBRT with two different fractionation schedules with concurrent TMZ.

3. METHODS

Eligibility Criteria

The Medical Ethics Review Board approval was sought for the study protocol and consent procedure. Patients aged 18-70 years with ECOG status less than 3 with a histologically proven systemic tumor, radiologically diagnosed brain metastases, and without a history of metastatectomy, radio-surgery, or chemotherapy in the previous three weeks and prior radiation to brain were eligible. Patient and tumor characteristics are as shown in.

Informed consent was taken. Patients were randomly assigned into two groups; whole brain radiation therapy with 40 gray/20 fractions (group A) and 30 gray/10 fractions (group B). Concurrent chemotherapy was given in both groups.

Radiation Therapy

For WBRT, the entire brain parenchyma and meningeal reflections were treated.

Chemotherapy

Half an hour before radiation therapy, patients in both arms received capsule Temozolomide (TMZ),75mg/m^2,fivedays a week, orally, under fasting condition, along with prophylactic oral antiemetic (ondansetron 8 mg OD) before TMZ.

Memory Function Assessment

Memory function assessment was done using P.G.I. Memory scale.

4. Data Analysis And Results

Data analysis was done using the statistical software SPSS15.0, A P value of less than 0.05 is taken as a significant relationship

Table 1: Age Distribution By Group

Group	Mean	SD	Min	Max
Study	52.68	8.86	36.0	67.0
Control	48.24	9.90	36.0	69.0

The mean age in the Study group was 52.68 years (±8.86), while it was 48.24 years (±9.90) in the Control group. In the context of this study, a comparable mean age between the two groups (Study: 52.68 years, Control: 48.24 years) ensures that age-related cognitive variability is minimized, allowing a fair assessment of the impact of radiation dose on memory function.

Table 2: Sex Distribution By Group

Group	Male	Female
Study	9	16
Control	17	8

There was a higher proportion of males in the Control group and more females in the Study group.

Table 3: ECOG Performance Status by Group

Group	0	1	2

Study	10	7	8
Control	10	9	6

Both groups had a similar distribution of ECOG scores, indicating comparable functional status at baseline. ECOG status is an indicator of functional capacity. The similar distribution across groups indicates that baseline functionality was matched, reducing the risk that physical performance differences could influence memory outcomes.

Table 4: Hemoglobin, TLC, DLC by Group

Group	Hemoglobin Mean	Hemoglobin SD	TLC Mean	TLC SD	DLC Mean	DLC SD
Study	12.91	1.25	7285.44	1695.03	57.04	10.27
Control	12.63	1.16	7206.32	1675.78	60.6	10.66

Hemoglobin, total leukocyte count, and differential leukocyte count were similar between groups, suggesting no significant hematological difference at baseline.

Table 5: Urea And Creatinine By Group

Group	Urea Mean	Urea SD	Creatinine Mean	Creatinine SD
Study	31.85	7.7	1.0	0.22
Control	29.53	9.0	0.96	0.23
P Value	0.288		0.494	

Mean values of urea and creatinine were marginally higher in the Study group, but the difference is not significant as the p value is >0.05.

Table 6: Comparison of Remote Memory Scores between Groups

Group	Mean	SD	p-value
Study	5.72	0.46	4.34
Control	5.0	0.41	

Table 7: Comparison of Recent Memory Scores between Groups

Group	Mean	SD	p-value
Study	5.0	0.0	0.0208
Control	4.52	1.05	

Table 8: Summary of All Memory Domains by Group

Memory Domain	Study Mean ± SD	Control Mean ± SD	p-value
Remote Memory	5.72 ± 0.46	5.00 ± 0.41	0.000
Recent Memory	5.00 ± 0.00	4.52 ± 1.05	0.021

Summary Of Results

1. Baseline Characteristics (Tables 1–5)

- **Age**: Mean age was slightly higher in the study group (52.68 ± 8.86 years) compared to the control group (48.24 ± 9.90), though not statistically significant.
- **Sex Distribution**: The study group had more females, while the control group had more males.
- **ECOG Performance**: Both groups had similar ECOG scores, suggesting comparable functional status.
- **Haematological & Renal Parameters**: No significant differences were found in haemoglobin, TLC, DLC, urea, or creatinine levels ($p > 0.05$ for all).

These findings indicate that the two groups were well matched at baseline, minimizing confounding in memory function assessment.

2. Memory Domain Comparisons (Tables 6-8)

Memory function was assessed using the **PGI Memory Scale** across two domains.

Statistically Significant Higher Scores In The Study Group (Long-Course Wbrt) Were Found For:

Memory Domain	p-value
Remote Memory	0.000
Recent Memory	0.021

DISCUSSION

Memory Domain	Present Study	Poojar et al. (2019)	Welzel et al. (2008)	Brown et al. (2016) / Gondi et al. (2014)
Remote Memory	Higher in long-course WBRT	Improved with long-course WBRT	Affected post-WBRT in verbal domains	Cognitive decline seen with WBRT; hippocampal sparing beneficial (Gondi)

This study aimed to evaluate baseline memory function in patients with brain metastases scheduled for either short-course or long-course Whole Brain Radiation Therapy (WBRT), utilizing the PGI Memory Scale.

Summary Of Main Findings

The study revealed that patients in the long-course WBRT group exhibited significantly better performance in both memory domains, including Remote & Recent Memory.

Clinical Implications

The superior baseline memory performance observed in the long-course WBRT group suggests that treatment planning may inherently favour patients with better cognitive reserve. This raises important considerations for clinical practice:

- **Routine Cognitive Assessment**: Implementing standardized cognitive evaluations, such as the PGI Memory Scale, before initiating WBRT could inform treatment decisions and identify patients at higher risk for cognitive decline.
- **Personalized Treatment Planning**: Tailoring WBRT regimens based on baseline cognitive function may optimize outcomes, balancing tumor control with quality of life considerations.
- **Informed Consent And Counselling**: Discussing potential cognitive risks associated with different WBRT schedules can aid in shared decision-making and set realistic expectations for patients and caregivers.

Strengths And Limitations

Strengths:

- **Novel Focus:** This study uniquely examines baseline memory function in patients scheduled for different WBRT regimens, addressing a gap in existing literature.
- **Validated Assessment Tool**: Utilization of the PGI Memory Scale, tailored for the Indian population, enhances the reliability of cognitive evaluations.
- **Comprehensive Analysis**: Incorporating correlations with clinical and laboratory parameters provides a holistic understanding of factors influencing cognitive function.

Limitations:

- **Sample Size**: The relatively small cohort may limit the generalizability of findings and the statistical power to detect subtle differences.
- **Cross-Sectional Design**: The absence of longitudinal follow-up precludes assessment of cognitive trajectories post-WBRT.
- **Potential Selection Bias**: Non-randomized group allocation may introduce bias, as patients with better baseline cognition could be preferentially assigned to longer treatment courses.

Future Directions

- **Longitudinal Studies**: Prospective research tracking cognitive changes over time post-WBRT can elucidate the temporal dynamics of neurocognitive effects.
- **Randomized Controlled Trials**: Randomizing patients to different WBRT schedules while controlling for baseline cognitive function would strengthen causal inferences.
- **Neuroprotective Strategies**: Investigating interventions such as hippocampal avoidance, pharmacologic agents like memantine, and cognitive rehabilitation programs may offer avenues to preserve cognitive function.
- **Integration Of Biomarkers**: Incorporating neuroimaging and molecular biomarkers could enhance the understanding of mechanisms underlying cognitive changes and identify at-risk individuals.

5. CONCLUSION

This study highlights significant differences in baseline cognitive performance, specifically in remote and recent memory domains, among patients receiving long-course versus short-course whole brain radiotherapy (WBRT) with concurrent Temozolomide. Patients scheduled for long-course WBRT demonstrated superior memory scores, suggesting the presence of greater cognitive reserve prior to treatment initiation.

While the observed cognitive advantage may not be directly attributable to the radiation fractionation schedule itself, these findings underscore the importance of incorporating baseline neurocognitive assessments into the clinical decision-making process. Tailoring WBRT regimens based on a patient's cognitive profile may help

optimize both oncologic control and quality of life.

Future prospective, randomized studies with post-treatment follow-up are warranted to evaluate the longitudinal impact of WBRT fractionation on memory function. Integrating cognitive screening tools, such as the PGI Memory Scale, into standard radiotherapy workflows could provide a valuable framework for personalized brain metastasis management.

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