



# Impact of Short Versus Long Course Whole Brain Radiation Therapy on Memory Function in Brain Metastasis Patients

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## Abstract

**Background:** Most common intracranial tumor in adults is brain metastasis. Different fractionation schedules used for whole brain radiation therapy are 20 gray/5 Fr, 30 gray/10 Fr, and 40 gray/20 Fr, 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) in patients with brain metastases.

**Methods:** A total of 20 patients, who were histologically proven primary and recently diagnosed brain metastases, with a RPA class of I/II, and satisfying eligibility criteria were taken into this study. Patients were randomly assigned to whole brain radiation therapy of 40 gray in 20 fractions (group A) and 30 gray 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, as well as at three months and six months of follow-up. Two groups were compared for with appropriate statistical tests.

**Results:** Patients in group A showed improvement in five domains of memory function (attention and concentration, remote and recent memory, mental balance and verbal retention for similar pair) during radiation therapy, compared to group B patients. However, deterioration of memory function was noted in both groups at 3- and 6-months post chemoradiation therapy.

**Conclusions:** Fourty Gy in 20 fractions given over four weeks with concurrent TMZ 75 mg/m<sup>2</sup> is a better and preferable treatment option for patients with brain metastasis with respect to memory function.

**Keywords:** Whole Brain Radiotherapy (WBR), Brain Metastases, Memory Function

## 1. Background

Metastasis to the brain is one of the most common intracranial tumors in adults. An important cause of morbidity and mortality in 10% to 30% of adult cancer patients is brain metastasis (BM) (1). As per the American Cancer Society, in the United States, each year 170000 cancer patients develop brain metastasis, with most of them having two or more metastases (2). Lung cancer is the most common primary cause of brain metastases and is accountable for nearly half of all secondary tumors of the brain. Other major primary tumors comprise of breast cancer, melanoma, and colorectal cancer.

Brain metastasis patients with different signs and symptoms range from an incidental imaging finding to changes in mental status, seizures, headache, dizziness, blurred vision, nausea, weakness or aphasia. Symptoms usually progress over a period of a few weeks. However, with tumors like malignant melanoma, thyroid car-

cinoma, renal cell carcinoma, and choriocarcinoma, patients may present with hemorrhage into the metastases, which can cause a more dramatic presentation (3). Patients are managed with symptomatic care and definitive treatment. Multiple lesions or widespread metastatic disease is seen in the majority of patients at presentation. Whole brain radiotherapy (WBRT) is the standard treatment (4, 5). SRS have the advantage over resection. With respect to overall survival no statistically significant is noted with different fractionation schedules and doses. With respect to tolerability, short treatment time, cost-effectiveness, and trend for better survival 30 gray/10 fractions have become the standard of care (6). Systemic chemotherapy in brain metastases patients is rapidly growing as a treatment option. Antonadou et al., suggested that concomitant whole brain radiotherapy and temozolomide improves quality of life (7).

The effect of WBRT on neurocognitive dysfunction and

dementia is poorly understood. A study conducted at Memorial Sloan Kettering Cancer Center demonstrated that patients surviving one year or more after WBRT had an 11% risk of dementia (8).

## 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 are evaluating memory function outcomes in patients receiving WBRT with two different fractionation schedules with concurrent TMZ.

## 3. Methods

### 3.1. Eligibility Criteria

The Medical Ethics Review Board approval was sought for the study protocol and consent procedure. Patients aged 18 - 70 years with Karnofsky performance status (KPS) of more than or equal to 70, 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 Table 1.

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.

### 3.2. Radiation Therapy

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

### 3.3. Chemotherapy

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

### 3.4. Memory Function Assessment

Memory function assessment was done using P.G.I. Memory scale before, during, and after the treatment, as well as at three months and 6 months of follow-up (Tables 2-8).

**Table 1.** Patient and Tumor Characteristics<sup>a</sup>

	Group A	Group B	P Value
<b>Total</b>	10 (100)	10 (100)	
<b>Age</b>			0.910
21 - 30	1 (10)	1 (10)	
31 - 40	2 (20)	1 (10)	
41 - 50	4 (40)	4 (40)	
51 - 60	2 (20)	4 (40)	
> 60	1 (10)	0 (0)	
<b>Gender</b>			1.000
Male	4 (40)	3 (30)	
Female	6 (60)	7 (70)	
<b>KPS</b>			1.000
70	2 (20)	2 (20)	
80	5 (50)	5 (50)	
90	3 (30)	3 (30)	
<b>Neurological deficit</b>			0.160
Yes	2 (20)	5 (50)	
No	8 (80)	5 (50)	
<b>Site of primary tumor</b>			1
Lung	8 (80)	7 (70)	
Breast	1 (10)	0 (0)	
Bronchogenic carcinoma	1 (10)	1 (10)	
Choriocarcinoma	0 (0)	1 (10)	
Metastasis of unknown origin	0 (0)	1 (10)	
<b>BSA</b>			0.532
< 1.3	0 (0)	2 (20)	
1.3 - 1.6	10 (100)	7 (70)	
> 1.6	0 (0)	1 (20)	
<b>Number of brain metastases</b>			1.000
1	1 (10)	1 (10)	
2 - 4	8 (80)	8 (80)	
> 4	1 (10)	1 (10)	

Abbreviations: BSA, body surface area; KPS, Karnofsky performance status.

<sup>a</sup>Values are expressed as No. (%).

### 3.5. Follow-up

Patients were followed-up for a period of six months' after chemo radiation therapy.

## 4. Results

### 4.1. Statistical Methods

Data analysis was done using the statistical software SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0, and

**Table 2.** Remote Memory (Maximum Score 6)

Remote Memory (Maximum Score 6)	Group A	Group B	P Value
Before RT	5.40 ± 0.70	5.10 ± 0.32	0.232
During RT	5.70 ± 0.48	5.10 ± 0.32	0.004**
After RT	5.70 ± 0.48	5.00 ± 0.47	0.004**
3 months	5.11 ± 0.93	4.43 ± 0.53	0.106
6 months	5.00 ± 0.00	4.50 ± 0.71	0.667

**Table 3.** Recent Memory

Recent Memory	Group A (Mean Rank)	Group B (Mean Rank)	P Value
Before RT	11.8	9.2	0.353
During RT	11.6	9.4	0.436
After RT	14.8	6.2	0.001
3 months	9.61	10.35	0.78
6 months	8.56	11.3	0.315

**Table 4.** Attention and Concentration

Attention and Concentration	Group A (Mean Rank)	Group B (Mean Rank)	P Value
Before RT	9.45	11.55	0.436
During RT	8	13	0.063
After RT	14.05	6.95	0.005
3 months	8.28	11.55	0.211
6 months	9.06	10.85	0.497

**Table 5.** Delayed Recall (Maximum Score 10)

Delayed Recall (Maximum Score 10)	Group A	Group B	P Value
Before RT	7.90 ± 0.88	7.90 ± 0.88	1.000
During RT	8.20 ± 0.92	8.00 ± 0.82	0.613
After RT	8.00 ± 1.05	7.90 ± 0.99	0.830
3 months	7.67 ± 1.22	7.86 ± 1.07	0.749
6 months	7.00 ± 0.00	8.00 ± 1.41	0.667

**Table 6.** Immediate Recall (Maximum Score 12)

Immediate Recall (Maximum Score 12)	Group A	Group B	P Value
Before RT	9.10 ± 1.52	8.80 ± 1.32	0.643
During RT	9.80 ± 1.69	8.90 ± 1.37	0.207
After RT	9.50 ± 1.72	8.70 ± 1.64	0.300
3 months	8.44 ± 1.67	8.43 ± 1.62	0.985
6 months	6.00 ± 0.00	9.50 ± 0.71	0.154

**Table 7.** Verbal Retention for Similar Pairs

Verbal Retention For Similar Pair	Group A (Mean Rank)	Group B (Mean Rank)	P Value
Before RT	11.45	9.55	0.481
During RT	10.25	10.75	0.853
After RT	14.45	6.55	0.002
3 months	8.78	11.1	0.4
6 months	9.22	10.7	0.604

**Table 8.** Verbal Retention for Dissimilar Pairs (Maximum Score 15)

Verbal Retention for Dissimilar Pairs (Maximum Score 15)	Group A	Group B	P Value
Before RT	10.40 ± 0.97	10.70 ± 1.06	0.517
During RT	10.70 ± 1.16	10.70 ± 1.06	1.000
After RT	10.70 ± 1.06	10.10 ± 1.79	0.374
3 months	8.89 ± 1.83	9.43 ± 0.79	0.481
6 months	8.00 ± 0.00	10.00 ± 0.00	-

R environment Ver.2.11.1. A P value of less than 0.05 is taken as a significant relationship.

### 5. Discussion

An ability to retain and reproduce intentionally perceived impression is memory (9, 10). This definition includes compartmental views of very short term, short term, and long-term memory. Working memory is often used to denote short term memory. Short-term memory allows a recall for a period of several seconds to a minute without rehearsal. Its capacity is also very much limited. Long-term memory can store much larger quantities of information for potentially unlimited duration (sometimes a whole life span). Its capacity is immeasurable. Information is encoded acoustically in short term memory and semantically in long term memory. Transient patterns of neuronal communication support short-term memory and is dependent on regions of the frontal lobe and the parietal lobe. On the other hand, long-term memory is supported by permanent changes in neural connections. Short term memory is consolidated into long term memory in hippocampus.

Recent research in humans showed that DNA methylation, or prions, are responsible for long-term memory storage (11). In the recognition memory task it is evaluated whether an individual had an encounter with a stimulus like a picture or a word before.

Ecognition memory tasks require individuals to indicate whether they have encountered a stimulus (such as a

picture or a word) before. In the recall memory tasks, participants are asked to retrieve previously learned information.

Neuro toxicity is noted in brain metastasis patients who have received WBRT, especially declarative memory. The study of Chang et al., observed a greater decline in memory [as demonstrated by the Hopkins verbal learning test revised (HVLT-R)] at four months, in the SRS plus WBRT group compared to SRS alone (12). This decline in memory has been described as part of a biphasic pattern of cognitive loss. Post WBRT initial deterioration was noted in multiple domains of cognitive function, which peaks around four months post radiation.

Their study of DeAngelis et al. (8), on 12 patients treated with WBRT (25 - 39 Gy in three to six Gy per fractions), dementia, ataxia, and incontinence was noted in all the patients at a median of 14 months after WBRT. However, actual incidence of radiation induced dementia is much lower in modern practice as smaller fraction sizes are used.

Studies using these regimens in conjunction with neurocognitive follow-up have suggested general stability in neurocognitive function for most patients in the short to medium term after whole brain radiotherapy in the absence of tumor recurrence. In addition, in our study, we noted the improvement in four domains of memory function in patients treated with two Gy per fraction during radiation therapy.

However, decline in memory function was noted in both groups at three and six months post treatment assessment of memory function. The short-coming of our study is the small population of patients. Hence it needs to be confirmed in a study with a larger population. In addition, an improvement in the memory function might be due to the specific location in the brain, hence it also needs to be analyzed further.

### 5.1. Conclusions

Therefore, we conclude that 40 Gy in 20 fractions given over four weeks, with concurrent TMZ, is better and a preferable treatment option for patients with brain metastasis with respect to memory function. However, it needs to be confirmed in a study with a larger population.

### Footnotes

**Conflict of Interests:** Authors have no conflict of interest to declare.

**Ethical Approval:** The Medical Ethics Review Board approval was sought for the study protocol.

**Funding/Support:** None.

**Patient Consent:** Informed consent was taken from the patients.

### References

1. Posner JB. *Neurologic complications of cancer*. Philadelphia: F. A. Davis Company; 1995.
2. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol*. 2007;**25**(10):1260-6. doi: [10.1200/JCO.2006.09.2536](https://doi.org/10.1200/JCO.2006.09.2536). [PubMed: [17401015](https://pubmed.ncbi.nlm.nih.gov/17401015/)].
3. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. *Cancer*. 1983;**52**(12):2349-54. doi: [10.1002/1097-0142\(19831215\)52:12<2349::aid-cncr2820521231>3.0.co;2-b](https://doi.org/10.1002/1097-0142(19831215)52:12<2349::aid-cncr2820521231>3.0.co;2-b). [PubMed: [6640506](https://pubmed.ncbi.nlm.nih.gov/6640506/)].
4. Mehta M, Noyes W, Craig B, Lamond J, Auchter R, French M, et al. A cost-effectiveness and cost-utility analysis of radiosurgery vs. resection for single-brain metastases. *Int J Radiat Oncol Biol Phys*. 1997;**39**(2):445-54. doi: [10.1016/S0360-3016\(97\)00071-0](https://doi.org/10.1016/S0360-3016(97)00071-0). [PubMed: [9308949](https://pubmed.ncbi.nlm.nih.gov/9308949/)].
5. Rutigliano MJ, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M. The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. *Neurosurgery*. 1995;**37**(3):445-53. discussion 453-5. doi: [10.1227/00006123-199509000-00012](https://doi.org/10.1227/00006123-199509000-00012). [PubMed: [7501109](https://pubmed.ncbi.nlm.nih.gov/7501109/)].
6. Murray KJ, Scott C, Greenberg HM, Emami B, Seider M, Vora NL, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: A report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys*. 1997;**39**(3):571-4. doi: [10.1016/S0360-3016\(97\)00341-6](https://doi.org/10.1016/S0360-3016(97)00341-6). [PubMed: [9336134](https://pubmed.ncbi.nlm.nih.gov/9336134/)].
7. Antonadou D, Paraskevaidis M, Sarris G, Coliarakis N, Economou I, Karageorgis P, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol*. 2002;**20**(17):3644-50. doi: [10.1200/jco.2002.04.140](https://doi.org/10.1200/jco.2002.04.140). [PubMed: [12202665](https://pubmed.ncbi.nlm.nih.gov/12202665/)].
8. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology*. 1989;**39**(6):789-96. doi: [10.1212/wnl.39.6.789](https://doi.org/10.1212/wnl.39.6.789). [PubMed: [2725874](https://pubmed.ncbi.nlm.nih.gov/2725874/)].
9. Pershad D, Wig NN. Reliability and validity of a new battery of memory tests. *Indian J Psychiatry*. 1978;**20**(1):76-80.
10. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes*. 2003;**1**(1):29. doi: [10.1186/1477-7525-1-29](https://doi.org/10.1186/1477-7525-1-29).
11. Miller CA, Sweatt JD. Covalent modification of DNA regulates memory formation. *Neuron*. 2007;**53**(6):857-69. doi: [10.1016/j.neuron.2007.02.022](https://doi.org/10.1016/j.neuron.2007.02.022). [PubMed: [17359920](https://pubmed.ncbi.nlm.nih.gov/17359920/)].
12. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol*. 2009;**10**(11):1037-44. doi: [10.1016/S1470-2045\(09\)70263-3](https://doi.org/10.1016/S1470-2045(09)70263-3). [PubMed: [19801201](https://pubmed.ncbi.nlm.nih.gov/19801201/)].