Title: Memantine for The Prevention of Radiation-Induced Cognitive Dysfunction in Brain Metastases Patients- A Randomized Placebo-Controlled Trial CTRI/2022/01/039599

Introduction

Brain metastasis (BM) is three to ten times more common than primary brain tumors. Patients with brain metastasis have relatively short average survival of 3 to 12 months. Patients with brain metastasis commonly have higher function impairment, like short-term memory loss, speech disability, reading disability, difficulty in understanding words, recognizing person and places(1,2). Radiation therapy (RT) is the standard of care in brain metastasis and a large proportion of brain metastasis patients with multiple brain lesions are earlier treated with whole-brain radiation therapy (WBRT). The disease itself and the radiation therapy (WBRT) may impair higher motor function (91%), hence affecting cognitive function and quality of life (QOL). Preservation of cognitive function is paramount in brain metastasis to preserve quality of life and hence different methodologies were considered. Hippocampal avoidance during WBRT (HAWBRT) is a newer and exciting technique essential to preserve memory and other neurocognitive functions by restringing the radiation dose delivered and radiation exposure to hippocampal areas. This maximizes the process of continuous neurogenesis and the formation of neurons that participate in the imprinting of new memory. HA WBRT has shown promise in the preservation of delayed memory in patients with brain metastasis. However, there are other domains in cognition such as executive function, language, fluency, orientation, recognition, attention, speech disability, visuospatial ability etc. needs to be preserved for the activity of daily living. Stereotactic radiosurgery (SRS), an advanced radiation technique is the present standard of care in brain metastasis patients with 1-3 lesions who are expected to survive for a longer period where neurocognitive function preservation is critical(3). Number of brain metastasis patients treated with WBRT and SRS are almost the same number since recent years. In a randomized trial conducted by Brown et al., reported cognitive deterioration of 91.7% in WBRT whereas in SRS patients were reported with 63.5% of the cognitive deterioration(4). Thus, preserving cognitive function post RT continues to remain a challenge despite the advent of contemporary practices, such as HA-WBRT and SRS.

Multiple pathophysiological mechanisms explain the cause of radiation-induced cognitive dysfunction. Majorly, N-methyl-D-aspartate receptors (NMDARs) mediated overexcitation causing cognitive impairment. If an agent can inhibit excessive pre-synaptic NMDA activation and control the intracellular calcium concentration without affecting normal physiological synaptic transmission, it will prevent cognitive impairment after radiation therapy(5). Memantine is one such agent. Memantine is an antagonist of NMDA-type glutamate receptors, inhibits extra synaptic NMDARs more potentially than synaptic NMDARs and it antagonizes the prolonged reflux of Ca 2+ ions through the NMDA channel, whilst maintaining normal synaptic transmission(6).

No prospective trials have been conducted so far to find out the role of memantine in SRS(7). Ironically, SRS is the standard of care among BM patients whose survival is expected to be more. Memantine with its inhibitory action on NMDA receptors will improve the QoL and cognitive functions among these cancer survivors. The present study aims to provide data on memantine in effectiveness in the degree of cognitive preservation, dosing, and tolerance and adverse events among BM patients. If found beneficial, the addition of memantine will allow treating patients with efficient radiation doses without compromising their neurocognitive function. Memantine helps to protect the neurocognition of the patient thereby not compromising on the dexterity in their area of work.

Objectives

Primary objective

- To determine whether the addition of memantine in radiotherapy for brain metastasis preserve the cognitive function at 6 months compared to a placebo

Secondary objectives

- Impact of memantine in preserving cognitive functions in brain metastatic patients treated with Whole Brain Radiotherapy (WBRT).
- Impact of memantine in preserving cognitive functions in brain metastatic patients treated with Stereotactic Radiosurgery (SRS).
- Impact of memantine in preserving cognitive functions in brain metastatic patients treated with Hippocampal Avoidance Whole Brain Radiotherapy (HA-WBRT).

- To assess the quality of life of patients receiving brain irradiation with or without memantine.
- To assess the safety and tolerability of Memantine.

Materials and methods

This trial has been registered in the clinical trial registry of India (CTRI/2022/01/039599) and was approved by the Institutional Ethics Committee of Amrita Institute of Medical Sciences and Research, Kerala, India (IEC-AIMS-2021-PHARM-338).

Written informed consent was obtained from all study patients. The key inclusion criteria were as follows: patients of either gender, aged 18 years and older; patients with a pathologically proven diagnosis of solid malignancy with BM visible on contrast-enhanced MRI (or CT for patients unable to have an MRI); patients who are able (sufficiently fluent) and willing to complete the cognitive function test and the QoL questionnaires in English, Malayalam, or Hindi; and patients with an ECOG performance status of 0, 1, or 2. The exclusion criteria included: patients who are not willing to participate in the study; patients with psychiatric illness, drug abuse, or mental retardation (premorbid intelligence quotient <70); patients with a history of prior cranial external beam radiotherapy; and patients currently using NMDA antagonists such as amantadine, ketamine, or dextromethorphan. Patients were screened by the radiation oncologist and a research scholar during the first consultation.

Sample size calculation and randomization

Sample size was calculated from the pilot study of 22 patients. Based on the mean change of Addenbrooke Cognitive Examination (ACE) score from baseline to post radiation therapy finding in brain metastatic patients receiving memantine (9.6±11.5) and placebo (-7.7±9.2) observed in a small pilot study with 22 samples and with 90% power and 95% confidence the minimum sample size is 8 in each group, totaling to 16 patients.

In accordance with the number of patients receiving different modalities of radiation therapy (three, in our institute) while expecting a 20% dropout/ death, a total of 65 samples in either of the two aforementioned arms, a total of 130 samples would be required for the study to be feasible. Randomization chart was developed using random sequence generation software with 1:1 ratio.

Treatment

Patients received 30 Gy of WBRT in 10 fractions of 2.5 Gy each, or 30 Gy in 10 fractions with a 5 mm margin in hippocampal-sparing WBRT, or SRS in a single session or 3-5 fractions. The administration of the study drug began no later than the third day of radiotherapy. Patients were randomly assigned to receive either memantine or a placebo with 1:1 ratio, orally for 24 weeks, with dose escalation over the first 4 weeks. In week 1, patients received a single 5 mg dose in the morning, followed by an additional 5 mg dose in the evening during week 2. In week 3, the morning dose was increased to 10 mg. The target dose from weeks 4 through 24 was 10 mg in the morning and 10 mg in the evening, for a total daily dose of 20 mg.

If a patient's creatinine clearance fell below 30 mL/min, the dose was reduced to 5 mg orally twice daily. If creatinine clearance dropped below 5 mL/min, the medication was withheld, with weekly laboratory monitoring. For patients with a serum creatinine level of 1.2, the dose escalation was limited to 5 mg twice daily, which was maintained for the entire 24-week period.

Assessment tools

A neuropsychologist performed NCA before treatment using the following measures (Table 1). The neurocognitive profile was evaluated using ACE which evaluates cognitive domains such as attention and orientation, memory (encompassing recall, anterograde memory, retrograde memory, and delayed recall), language, and visuospatial abilities. The total ACE score ranges from 0 to 100, with domain-specific allocations as follows: attention and orientation (18 points), memory (35 points), fluency (14 points), language (28 points), and visuospatial skills (5 points). A score below 82 indicates cognitive impairment(8).

QoL was assessed using the EORTC QLQ-C30, version 3, and BN20. The QLQ-C30 is a core measure designed for all patients and includes five functional scales—physical, role (daily life), emotional, cognitive, and social; three symptom scales—fatigue, nausea and vomiting, and pain; and six single-item scales—dyspnoea, insomnia, appetite loss, constipation, diarrhoea, the financial impact of the tumour and treatment, and overall quality of life. The QLQ-BN20 consists of 20 items that assess visual disorders, motor dysfunction, communication deficits, various disease symptoms (e.g., headaches and seizures), treatment-related toxic effects (e.g., hair loss), and future uncertainty. Items from both questionnaires were scaled and scored using the

recommended EORTC procedures. Raw scores were transformed to a linear scale ranging from 0 to 100. Higher QLQ-C30, scores in functional domains indicate better functioning, while higher scores in symptom domains indicate more symptoms. Therefore, higher functional scores and lower symptom scores reflect improved QoL. Conversely, for the QLQ-BN20, lower scores indicate fewer symptoms and better QoL. The patients themselves filled QoL questionnaires, (with help from caregivers if required) during their first few visits (before radiation therapy)(9,10).

Statistical analysis

We conducted all statistical analyses using IBM SPSS Statistics version 26.0. Descriptive statistics were employed to assess the patient cohort's baseline demographic, clinical, treatment, cognitive, and QoL parameters. The neurocognitive status of patients was categorized based on the mean ACE score of 75.19. We classified patients with a score of 75.19 or above as having normal cognitive performance. Cognitive decline was further categorized as follows:

Mild Cognitive Decline: A decline of 1 SD (18.67) from the mean ACE score of 75.19.

Moderate Cognitive Decline: A decline of 2 SDs (37.34) from the mean ACE score.

Severe Cognitive Impairment: Scores falling below the 2 SD decline threshold.

In addition to mean ACE scores, we computed Z-scores for the ACE and its specific domains. The Z-score was calculated using the formula $x - \bar{x} \ / \ SD$

Where $\bar{x}$ represents the mean score from the dataset.

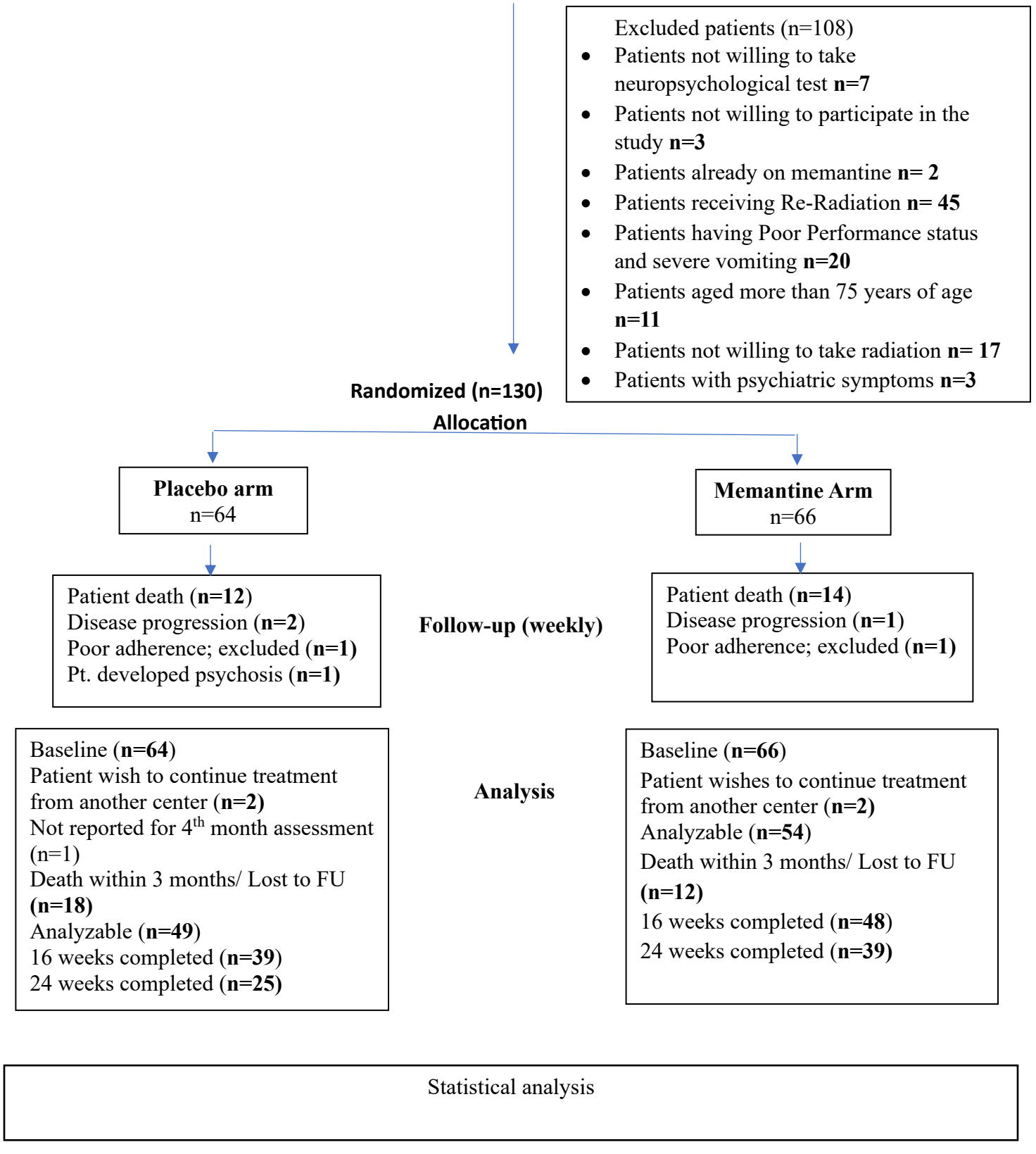
We performed univariate analysis to explore the relationship between predisposing factors and the four categories of cognitive status in BM patients. The subsequent multinomial logistic regression analysis was performed for the variables that demonstrated significant differences ($p < 0.1$) in univariate analysis.

Since the baseline cognitive profiles of the placebo and memantine groups were comparable, the mean change in cognitive scores was used to compare the difference in cognition between the groups. An independent samples t-test was performed to estimate the effectiveness of memantine between the groups. A p-value of less than 0.05 was considered statistically significant. Changes in quality of life were also compared using an independent samples t-test.

Results

Figure 1: CONSORT

Radiation-receiving Brain metastatic patients **screened** in OPD from **1st May 2022 to 8th July 2024 n= 238**



Between May 2022 and July 2024, a total of 130 patients were randomly assigned to receive radiation therapy (RT) with either memantine or a placebo. The type of RT was determined based on the tumor size, number of metastases, and the patient's performance status (figure 1). BM was prominent in the 51 to 60 age category group. 61.5% were female. Seventy-five (48.4%) patients had synchronous BM. Twenty-eight (21.5%) patients were treated with WBRT, 75 (57.6%) with radiosurgery (SRS) and only 27 (20.7%) received hippocampal avoidance whole brain radiation therapy (HAWBRT). Twenty-five (19.2%) patients underwent surgery before RT but NCA and QoL were done after 2 to 3 weeks of post-surgery. Forty-three (33.0%) patients presented with carcinoma lung, and forty-nine (37.6%) patients presented with breast primary and one patient reported rare primary of the pancreas. The treatment groups were well-balanced and had no significant differences in demographic, baseline neurologic function, or tumor-related characteristics (Tables 1 and 2).

Table 1: Baseline Characteristics of Eligible Patients

Characteristics	**Placebo arm (n=64)**	**Memantine arm (n=66)**
Age (mean ± SD)	56.59±9.4	56.70±10.45
Gender n (%)		
Male	24 (37.5)	25 (37.8)
Female	40 (62.5)	40 (60.6)
Karnofsky Performance Scale n (%)		
70	4 (6.25)	1 (1.51)
80	21 (32.8)	21 (31.8)
90	21 (32.8)	29 (43.9)
100	18 (28.1)	15 (22.7)
Family History n (%)		
Yes	20 (31.2)	18 (27.2)
No	44 (68.7)	48 (72.7)
Social history n (%)		
Alcoholic		
Yes	8 (12.5)	8 (12.1)

No	56 (87.5)	58 (87.8)
Smoking and tobacco n (%)		
Yes	8 (12.5)	13 (19.6)
No	56 (87.5)	53 (80.3)
Primary disease site n (%)		
Common		
Lung	21 (32.8)	22 (33.3)
Breast	25 (39.0)	24 (36.3)
Colon and Rectum	2 (3.12)	5 (7.57)
Thyroid	3 (4.68)	2 (3.03)
Melanoma	2 (3.12)	1 (1.51)
Kidney	3 (4.68)	2 (3.03)
Uncommon Primary site n (%)		
Ovary	3 (4.68)	3 (4.54)
Bladder/ Urothelium	1 (1.56)	1 (1.51)
Endometrium and uterus	2 (3.12)	2 (3.03)
Stomach	0 (0)	1 (1.51)
Liver	1 (1.56)	1 (1.51)
Rare primary site n (%)		
Pancreas	1 (1.65)	0 (0)
Number of lesions n (%)		
Single	17 (26.5)	19 (28.7)
2	12 (18.7)	13 (19.6)
=>3	33 (51.5)	33 (50)

Table 2: Baseline Treatment Parameters of Eligible Patients

Recursive Partitioning Analysis (RPA) Class n (%)		
characteristics	**Placebo arm**	**Memantine arm**
Class 1	34 (53.1)	28 (42.4)
Class 2	30 (46.8)	37 (56.0)
Prior surgery n (%)		
Done	9 (14.0)	16 (24.2)
Not done	55 (85.9)	50 (75.7)
Prior Chemotherapy n (%)		
Yes	37 (57.8)	41 (62.1)
No	21 (32.8)	18 (27.2)
Prior steroids n (%)		
Yes	31 (48.4)	22 (33.3)
No	28 (43.7)	37 (56.0)
Sites of metastases n (%)		
Brain	37 (57.8)	44 (66.6)
Brain and other sites	27 (42.1)	22 (33.3)
Type of Radiation therapy n (%)		
SRS	40 (62.5)	35 (53.0)
WBRT	13 (20.3)	15 (22.7)
HAWBRT	11 (17.1)	16 (24.2)
Presentation of metastases n (%)		
Synchronous	20 (31.25)	24 (36.3)
Metachronous	44 (68.7)	42 (63.6)

Baseline Addenbrooke Cognitive Examination (ACE) scores were comparable (74.64±19.2 and 77.5±14, p-value 0.48) (table 3)

Table 3: Baseline Cognitive Parameters of Enrolled Patients

Cognitive assessments	**Placebo Arm**	**Memantine Arm**
ACE (mean ± SD) (0-100)	74.64±19.29	77.53±14.01
Orientation (0-10)	8.47±2.12	8.66±1.56
Attention (0-8)	6.33±1.97	6.28±1.88
Memory (0-35)	23.58±7.29	23.79±6.62
Verbal Fluency (0-14)	9.16±2.89	9.64±3.01
Language (0-28)	25.50±4.13	25.83±2.42
Visuospatial abilities (0-5)	2.89±1.75	2.83±1.68
MMSE (0-30)	24.75±5.40	25.21±4.02
ACE- Addenbrooke cognitive examination; MMSE- Mini mental state examination		

NEURO-COGNITIVE OUTCOME

Table 4: Changes in median cognitive score from baseline

Week 16	**Placebo Arm (Median (IQR))**	**Memantine Arm (Median (IQR))**	**P value**
ACE	-5 -15 to 4	0 0 to 9	*<0.001*
Attention	0 -2 to 0	0 0 to 1.75	*<0.001*
Orientation	-5 -1.75 to 0	0 0 to 0	*0.002*
Memory	-1 -3 to 0.75	0 0 to 3.75	*0.005*
Verbal Fluency	-1 -2.75 to 0	0 0 to 1.5	*<0.001*
Language	0 -1.75 to 0	0 0 to 0	*0.07*
Visuospatial abilities	0 -1 to 0	0 0 to 1	*<0.001*

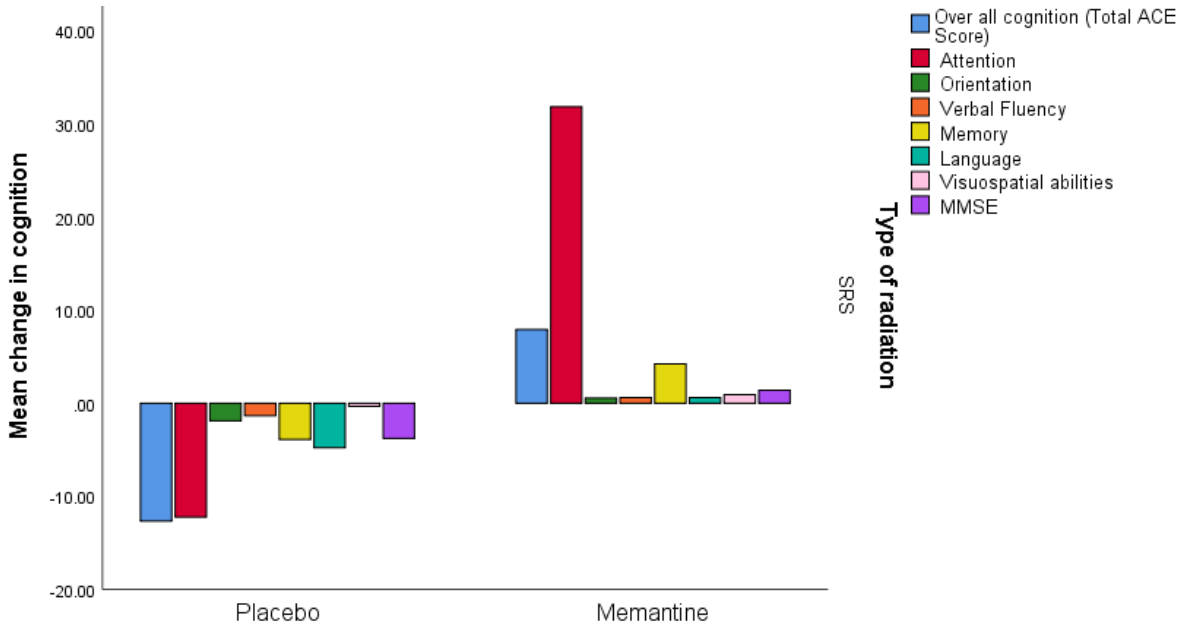
MMSE	-2.5 -5 to 0	0 0 to1	*<0.001*
Week 24			
ACE	-7 -13.5 to -2	4 0 to 10	*<0.001*
Attention	-1 -4 to 4	1 -1 to 5	*<0.001*
Orientation	-1 -2 to 0.5	0 0 to 1	*<0.001*
Memory	-2 -5 to 2.5	2 0 to 5	*0.008*
Verbal Fluency	-1 -2.5 to 0	0 0 to 2	*0.007*
Language	0 -4 to 0	0 0 to 1	*0.01*
Visuospatial abilities	-1 -3 to -1	0 0 to 1	*0.001*
MMSE	-3 -6 to -0.5	0 -2 to 0	*<0.001*

There was a decline in ACE score in the placebo arm (median decline of 5) compared with the score in the memantine arm (median of no change) at 16 weeks and the difference showed statistical significance of <0.001. There was also a trend of declining scores of each domain in placebo arm and improvement in memantine arm. At 24 weeks, the median decline of 7 scores reported in placebo group, whereas an improvement in scores of 4 in memantine group (p=<0.001) (table 4).

Table 5: Median change in cognitive functions in brain metastatic patients treated with Stereotactic Radiosurgery (SRS).

Cognition	Placebo Arm	Memantine Arm	P value
At Week 16			
ACE	**-3** **-9.5 to 0**	**0.5** **0 to 10**	***<0.001***
At Week 24			
ACE	**-6.5** **-14.7 to -1.5**	**3** **0 to 7.5**	***0.001***

Figure 2: change in neurocognitive outcome after receiving memantine

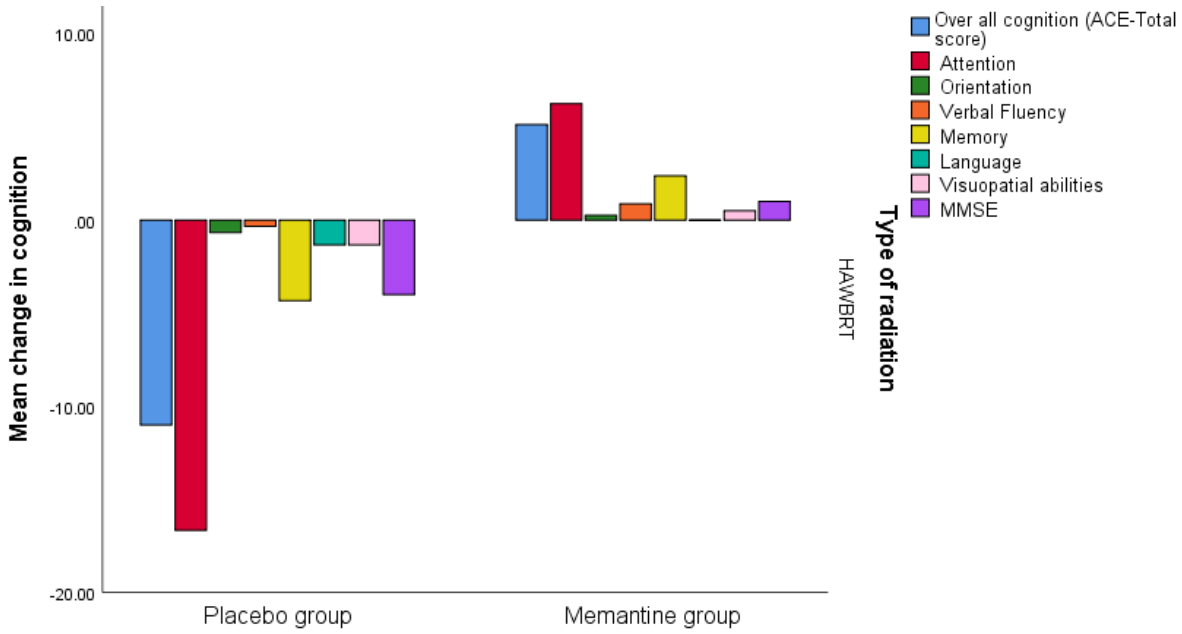


There was a median decline of 3 in cognitive function score in placebo arm whereas score of 0.5 increase reported in memantine arm at 16 weeks after SRS. However, in 24 weeks, there was a 6.5 score decline in placebo arm and a score of 3 increase in memantine. The median change in neurocognitive function among these two groups at 16 weeks and 24 weeks showed a statistical significance with a p value of <0.05 (table 5) (figure 2).

Table 6: Median change in cognitive functions in brain metastatic patients treated with hippocampal avoidance whole brain radiation therapy (HA-WBRT).

Cognition	Placebo Arm	Memantine Arm	P value
At Week 16			
ACE	**0** **-19 to 10**	**0** **-1 to 3**	**0.78**
At Week 24			
ACE	**-13** **-20 to 0**	**0** **0 to 3**	***0.02***

Figure 3: Change in neurocognitive function after HAWBRT



There was no difference in cognitive function score in placebo arm and memantine arm after HAWBRT at 16 weeks (p=0.78). However, in 24 weeks, there was a decline of 13 scores in placebo arm and no change in memantine arm (table 6 and figure 3).

Table 7: Median change in cognitive functions in brain metastatic patients treated with whole brain radiation therapy (WBRT).

Cognition	Placebo Arm	Memantine Arm	P value
At Week 16			**0.002**
ACE	-13 -22 to -3	0 0 to 12	
At Week 24			***0.009***
ACE	-6 -12 to -3	2 0 to 15	

There were 13 declines in cognitive function score in placebo arm whereas no median change reported in memantine arm at 16 weeks. However, in 24 weeks, there was a 6 score decline in placebo arm and 2 score increase in memantine. The differences were statistically significant.

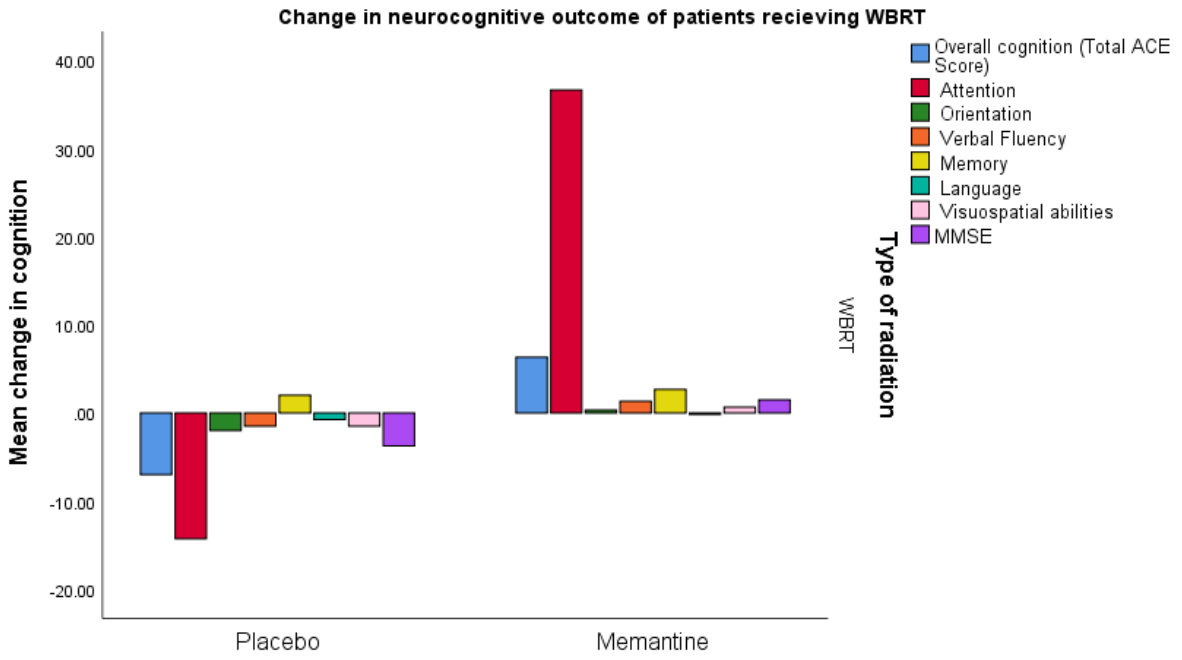


Table 8: Neurocognitive outcome with respect to location of brain metastatic lesion

Location of brain metastases	Placebo Arm	Memantine Arm	P value
Right cerebellum	-3 (-16.5 to2.5)	3 (0 to 17)	*0.026*
Left cerebellum	-2 (-13 to 0)	3 (0 to 8)	*0.026*
Right frontal	-3 (-9 to 0)	1.5 (3.5 to 7)	0.27
Left frontal	-7 (-11 to -3)	2.5 (0 to 16)	*0.03*
Right occipital	-2.5 (-5.2 to -0.5)	2 (0 to 13)	*0.025*
Left occipital	-1.5 (-3 to 0)	0 (0 to 13)	0.171
Brainstem	-1.5 (-15 to 5.25)	0 (0 to 18.75)	0.442
Right parietal	-5 (-18 to 0)	0 (-5 to 0)	*0.02*
Left parietal	-9 (-13 to -0.2)	3 (0 to 20)	*0.03*
Medial temporal	-18 (-36 to 0)	0 (0 to 13)	0.248
Near to hippocampus	-8 (-36 to 0)	0 (0 to 13)	0.248
Left temporal	-1.5 (-11.2 to 5.25)	2.5 (0 to 10)	0.157
Right temporal	-8.5 (-14 to -3)	1 (0 to 2)	0.121

Table 9: Neurocognitive outcome with respect to number of brain metastatic lesion

Number of brain lesions	Placebo Arm	Memantine Arm	P value
Single lesion	-9 (-57 to 0)	4 (0 to 5)	*0.017*
2	-7 (-14 to 0)	10.50 (2.25 to 21.75)	*0.034*
Multiple lesions	-3 (-13 to 0)	2.5 (0 to 11.25)	*<0.001*

Correlation between the predisposing factors and cognitive dysfunction of brain metastatic patients

Variables with a p-value of less than 0.1 in the univariate analysis (ECOG, employment at the time of assessment, education, hypertension, presentation of metastases, RPA class, lesions in the left temporal lobe, right occipital lobe, left occipital lobe, prior surgery, prior chemotherapy) were included in the multinomial logistic regression analysis. The risk for severe cognitive impairment was significantly lower in patients with above-graduate education compared to those with below-graduate education (OR = 0.002, 95% CI: 0.57 to 0.73; p = 0.03). Hypertension and lesions in the left temporal lobe were also significant risk factors for cognitive impairment, with OR = 52.08 (95% CI: 1.88 to 1441.3), p = 0.02, and OR = 71.40 (95% CI: 1.16 to 4393.2), p = 0.04, respectively (table 10).

Table 10: Multinomial logistic regression analysis to determine the relationship between functional outcomes and demographic and clinical predictors.

Cognitive dysfunctional status	Predisposing factors	Odds ratio	Lower bound-upper bound	P value
Mild cognitive impairment (74-56)	Employment			
	Working	0.22	0.04 to 1.18	0.07
	Not working	1		
	ECOG			
	0	0.05	0.09 to 0.36	0.003
	1	0.62	0.14 to 2.60	0.51
	2	1		
	Prior surgery			
	Done	1	0.02 to 0.41	0.002
	Not done	0.09		
Severe cognitive impairment (<37)	Education			
	Above graduate	0.002	0.57 to 0.73	0.03
	Below graduate	1		
	Hypertension			
	Present	52.08	1.88 to 1441.3	0.02
	Absent	1		
	Left temporal			
	Present	71.40	1.16 to 4393.2	0.04
	Absent	1		

QUALITY OF LIFE OUTCOMES

Table 11: Change in the quality-of-life outcome of enrolled patients using EORTC QLQ C-30 Questionnaire

Domains	Placebo Arm	Memantine Arm	P Value
At 16 weeks			
Global Health Status	-11.90±18.11	16.02±22.42	*<0.001*
Physical Functioning	-15.71±33.75	14.87±20.93	*0.005*
Role Functioning	-4.76 ±43.47	25.64±22.16	*0.05*
Emotional Functioning	-10.71±43.90	39.79 ±28.69	*0.002*
Social Functioning	-3.57 ±41.43	39.74 ±29.29	*0.028*
Cognitive Functioning	-25 ±25.10	28.20 ± 28.36	*0.007*
Fatigue	2.38±31.17	-32.47±28.49	0.07
Nausea & Vomiting	13.09±42.95	-1.28±24.01	0.114
Pain	2.38±36.31	-30.76±27.02	0.018
Dyspnoea	7.14±37.39	-10.25±25.03	0.258
Insomnia	16.66±53.50	-33.3±47.14	0.014
Loss of Appetite	26.19±49.23	-15.38±29.23	0.024
Constipation	16.66±58.10	-23.07±47.8	0.07
Diarrhoea	19.04±44.74	-5.1±35.60	0.115
Financial difficulty	11.90±33.60	23.09±47.80	0.39

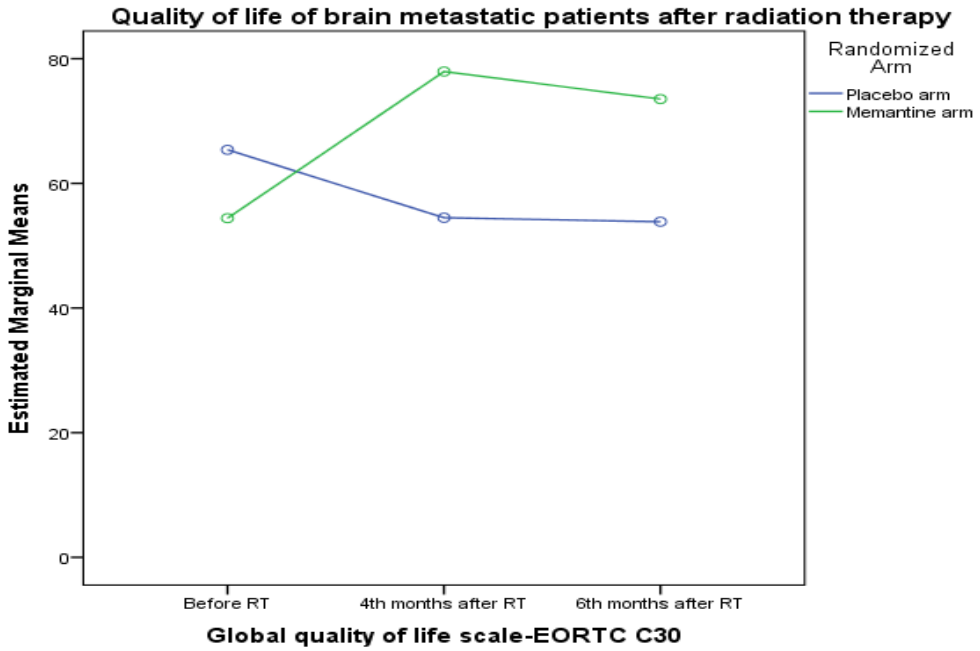


Table 12: Quality of life -Brain Neoplasm Module

Domains	Placebo arm	Memantine arm	P value
At 24 weeks			
Future uncertainty	0.14±1.07	-1.13±0.69	*0.016*
headache	0.07±1.38	-1.05±1.18	0.12
visual disorder	0.83±1.01	-0.5±0.52	0.06
seizures	0.42±1.22	-0.15±0.37	0.18
motor dysfunction	0.285±1.01	-0.51±0.42	0.05
communication deficit	0.97±0.70	-0.61±0.59	*0.001*
drowsiness	0.28±1.13	-0.7±1.09	0.06
Hair loss	0.57±1.22	-0.15±0.89	0.06
itchy skin	0.42±1.34	-0.23±0.43	0.29
bladder control	0.21±0.89	-1.2±1.30	0.06

Among participants, 115 patients (88.4%) completed the questionnaire independently, while 15 patients (11.5%) required assistance. EORTC QLQ C30 and BN20 showed significant differences between the placebo arm and memantine arm especially in physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning etc. Overall quality-of-life scale reported moderate quality of life in placebo arm and good quality of life in memantine arm.

Tolerability, adverse events, and serious adverse events reported

Adverse Events n (%)	**Placebo Arm**	**Memantine group**
Fatigue	29 (61.7)	23 (50)
Loss of appetite	6 (12.7)	15 (32.6)
Gastric irritation/ Belching	0	2 (4.34)
Breathlessness	2 (4.25)	1 (2.17)
Headache	4 (8.51)	3 (6.52)
Facial puffiness	2 (4.25)	2 (4.34)
Pedal oedema	2 (4.25)	2 (4.34)
Heaviness in head	4 (8.51)	3 (6.52)
Imbalance	6 (12.7)	5 (10.8)

Constipation	5 (10.6)	8 (17.3)
Vomiting	4 (8.51)	3 (6.52)
Serious Adverse Events n (%)		
Death	11 (23.4)	13 (28.2)

Grade 2 to 3 events were reported for 44 (39.7 %) (21 patients in placebo arm and 23 patients in memantine arm) of patients presented with common side effects being fatigue, loss of appetite, constipation, and gastric irritation. Loss of appetite and gastric irritation were prominently reported in the memantine arm. Eight patients had clinically significant loss of appetite and dose had reduced to 5 mg BD. No grade 5 treatment-related events were reported. There were no statistically significant differences between the treatment arms (0.253).

Discussion

Cognitive deterioration was evident among patients even before the initiation of radiation therapy. Among the study participants, 78 patients (60.0%) exhibited normal cognitive function with ACE scores of 75 or higher. A cognitive decline of 1 standard deviation (SD) was observed in 37 patients (28.5%), with scores ranging from 56 to 74. A decline of 2 SDs was noted in 8 patients (6.2%), with scores between 38 and 55. Severe cognitive impairment, characterized by scores below 37, was present in 7 patients (5.4%).

The treatment options for cognitive sequelae following cranial irradiation remain very limited(11). Memantine, an NMDA receptor antagonist, preferentially inhibits extra-synaptic NMDA receptors (NMDARs) more effectively than synaptic NMDARs, thereby minimizing excitotoxicity while preserving the transient physiological activation of synaptic NMDARs(12). Only a few trials have assessed the efficacy of memantine in preserving cognitive function following whole-brain radiation therapy (WBRT) (Brown et al., 2013, 2020; Wong et al., n.d.)(5,13,14). In the randomized controlled trial (RTOG 0614), memantine was well-tolerated and showed a trend toward better cognitive function over time in patients receiving WBRT, although the p-value for the primary endpoint of delayed recall at 24 weeks was only borderline significant(5). This is likely because radiation-induced cognitive dysfunction in WBRT is caused by multiple pathophysiological

mechanisms, including hypoxic-ischemic cascades, demyelination, neuroanatomical damage, neuroinflammation, and dysfunction of the limbic and hypothalamic systems(6).

Despite the National Comprehensive Cancer Network (NCCN) guidelines recommending the use of memantine with WBRT (Brown et al., 2013), the level of evidence remains 2, with only borderline significance. This may contribute to the under-prescription of memantine in WBRT(15).

The present study suggests that memantine offers more protective benefits for brain metastasis patients receiving stereotactic radiosurgery (SRS). Several theories, such as neuroinflammation, impaired hippocampal neurogenesis, and vascular damage, have been proposed to explain the mechanisms of radiation-induced cognitive dysfunction. Among these, vascular damage is a major predisposing factor for cognitive impairment in patients receiving SRS, as they are particularly susceptible to ischemia and radiation necrosis. Exposure of the brain to ionizing radiation affects small blood vessels, leading to small vessel disease. Endothelial cell loss begins with radiation therapy and continues for several months, causing remaining blood cells, including platelets, to adhere to the exposed matrix, forming clots. Reduced blood supply to the brain results in ischemia, which can lead to brain tissue necrosis(16).

When vascular insufficiency leads to cerebral ischemia, extracellular glutamate levels increase. Glutamate, the primary excitatory neurotransmitter involved in learning, memory, and neuronal plasticity, predominantly affects the cortical and hippocampal regions. In normal physiological states, glutamate activates three types of receptors, one of which is the N-methyl-D-aspartate receptor (NMDAR), an ionotropic, voltage-dependent receptor expressed throughout the brain, including the dorsolateral prefrontal cortex, amygdala, hippocampus, and ventral tegmental areas. NMDARs are primarily blocked by magnesium ions at resting membrane potentials and have high calcium ion permeability. During postsynaptic depolarization, magnesium ions are expelled from the channel, increasing calcium permeability and activating synaptic NMDAR activity.

NMDARs are located in both synaptic and extra synaptic regions of the brain. Vascular insufficiency following radiation therapy can cause ischemia, increasing the release of glutamate and the influx of excessive calcium into cells. This influx activates extra synaptic NMDARs, shifting

the balance from synaptic to extra synaptic NMDAR activity, resulting in neurotoxicity and neuronal death. Therefore, controlling intracellular calcium concentration is crucial for neuronal survival and function. An agent that antagonizes extra synaptic NMDAR activity and prevents excessive calcium influx could preserve cognitive function.

Memantine acts as an antagonist of the NMDA subtype of glutamate receptors by binding to phencyclidine sites within the channels, closing the ion channels, and preventing the entry of excess calcium into the cells, thereby helping maintain normal membrane potential (-70 mV) (Brown et al., 2013; Wong et al., n.d.). This prevents over-excitability and cell death associated with vascular ischemia, preserving neurocognitive function in brain metastasis patients treated with focal radiation, such as stereotactic radiosurgery(17).

Memantine was well-tolerated in this population of patients with brain metastases, with a side effect profile essentially equivalent to that of the placebo, except for a loss of appetite. Due to this side effect, 8 patients had to reduce their dose from 20 mg to 10 mg. Other trials have also found memantine to be well-tolerated, but loss of appetite or dose reduction has not been reported in these studies, even among elderly dementia patients with multiple comorbidities and polypharmacy(18).

Furthermore, patients with better prognostic factors and longer expected survival were more likely to benefit from memantine. This cohort is best represented by the SRS group, which typically includes patients with a more favourable prognosis and an anticipated longer survival duration.

Impact of the research in the advancement of knowledge or benefit to mankind

This study demonstrates the significant impact of memantine on cognitive function preservation and quality of life in patients with brain metastases undergoing radiation therapy. The changes in ACE scores at 4 and 6 months post-radiation therapy were markedly different between the placebo and memantine arms, with scores of -5 (-15 to 4) and 0 (0 to 9) (p-value < 0.001), and -7 (-13.5 to -2) and 4 (0 to 10) (p-value < 0.001), respectively. In the SRS cohort (patients who are expecting to live longer), the changes in ACE scores at 4 and 6 months were -3 (-9.5 to 0) and 0.5

(0 to 10) (p-value < 0.001), and -6.5 (-14.7 to -1.5) and 3 (0 to 7.5) (p-value < 0.001) for the placebo and memantine arms, respectively.

These findings indicate that patients in the memantine arm experienced statistically significant cognitive preservation compared to those receiving placebo. The use of memantine also led to improved QoL for patients with brain metastases receiving SRS. The results of this study advance current knowledge by providing strong evidence for the use of memantine as a neuroprotective agent in this patient population, potentially influencing clinical practice guidelines. This research contributes to improving patient outcomes by offering a therapeutic strategy to mitigate cognitive decline, thereby enhancing the quality of life for individuals affected by brain metastases.

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