List of publications

1. Surendran HP, Dutta D, Kalavagunta S et al., A Systematic Review and Meta-analysis to Elucidate the Dosing and Efficacy of Hippocampal Avoidance Whole Brain Radiotherapy (HA-WBRT) to Preserve the Neuro-Cognitive Functions among Brain Metastasis Patients- Submitted to journal of Neuro-Oncology (Under review)
2. Dutta D, Surendran HP, Kalavagunta S, Sasidharan A, Narmadha MP. Audit of presentation, primary site and pattern of treatment in 778 Indian patients with brain metastases. Neurology-India
3. Surendran HP, Sah SK, Louis DM, et al. Efficacy of memantine in preventing neurocognitive dysfunction induced by radiation therapy in patients with brain metastases: A systematic review of clinical trials. *Semin Oncol*. 2023;50(3-5):113-122. doi: 10.1053/j.seminoncol.2023.09.004
4. Surendran HP, Narmadha MP, Kalavagunta S, Sasidharan A, Dutta D. Preservation of cognitive function after brain irradiation. *J Oncol Pharm Pract*. 2022;28(5):1182-1188. doi:10.1177/10781552221077037
5. Surendran HP, Sah SK, Louis DM, Dutta D. CO104Efficacy of memantine in preventing neurocognitive dysfunction induced by radiation therapy in patients with brain metastases: a systematic review of clinical trials.*Value in health*, https://doi.org/10.1016/j.jval.2022.04.200
6. Louis DM, Sah SK, Surendran HP. CO70 Change in KI-67 Index in Patients Receiving Preoperative Endocrine Therapy Among Hormone Positive Breast Cancer Patients: A Systematic Review and Meta-Analysis. *Value in health.* 10.1016/j.jval.2022.04.168
7. Louis DM, DK V, Surendran HP CO102 Effectiveness of Short Term Neoadjuvant Endocrine Therapy on KI67 in Luminal Breast Cancer. *Value in health.* https://doi.org/10.1016/j.jval.2022.04.198
8. Surendran HP, Louis DM. PCR154 Assessment of the Impact of an ARIVU-IFK Software in Public Education about Infectious Diseases, Antibiotic Usage and Resistance in India. *Value in health.* https://doi.org/10.1016/j.jval.2022.04.1497
9. Surendran HP*,* Louis DM et al., Effect of Antenatal Betamethasone on Respiratory Distress Syndrome in Preterm Neonate. *Research Journal of Pharmacy and Technology.2022;15(4):1533-doi:10.52711/0974-360X.2022.00255*

10. Louis DM, Surendran HP, Sah SK. Assessment of clinical outcome and their risk factors in patients with stroke. Global journal of research analysis. VOLUME - 10, ISSUE - 04, APRIL - 2021 • PRINT ISSN No. 2277 - 8160 • DOI: 10.36106/gjra
11. Surendran HP, Naushad N, et al., Antenatal use of Corticosteroids to Prevent Respiratory Insufficiency in Preterm Babies, Asian Journal of Pharmaceutical Education and Research.2020. DOI: 10.38164/AJPER/9.4.2020.19-31

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Efficacy of memantine in preventing neurocognitive dysfunction induced by radiation therapy in patients with brain metastases: A systematic review of clinical trials

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ABSTRACT

Purpose: About 50%–90% of patients with brain metastases who receive radiation therapy experience cognitive impairment. This systematic review aims to gather credible sources of comprehensive information on the efficacy of memantine in preventing cognitive dysfunction.

Methods: A comprehensive review conducted in compliance with the PRISMA statement and systematic search was performed across five databases included PubMed®, Embase®, Scopus®, Cochrane Library®, and ClinicalTrial.gov.in from inception until November 2021.

Results: A total of four eligible studies were selected in this review that included 1,444 patients with brain metastases who received radiation therapy (Intervention group [n = 729] and control group [n = 715]). Overall, three of the four studies reported some improvement in neurocognitive function in at least one or more parameters such as recall and recognition ($P = .39$, $P = .10$ and $P = .05$), verbal fluency ($P = .03$ and $P < .0001$), complex attention ($P = .59$) executive function ($P = .92$) and normal appearing white matter ($P = .01$) following memantine therapy compared to control group. Further, two of the four studies reported an improvement in the patients' quality of life following memantine therapy compared to the control group, and there was no significant difference in the toxicity profile of the interventional compared to the control group as reported from two studies.

Conclusion: This review embraces the comprehensive evidence that the use of memantine therapy in patients with brain metastases to prevent radiation-induced neurocognitive dysfunction has a modest and statistically significant beneficial impact in improving quality of life and preserving some neurocognitive function without any complications. Pending the completion of additional ongoing studies, one can argue that memantine is a reasonable treatment to consider in patients with brain metastases while they receive whole brain radiation therapy.

Introduction

Brain metastases, being the most common intracranial tumours in adults, account for more than 50% of brain tumors [1–3]. In recent years, the incidence of brain metastasis has increased as a result of improvements in the detection of small metastases using magnetic resonance imaging (MRI) as well as the increase in the survival rates of patients with solid tumors [4,5]. Additionally, the survival of patients with brain metastasis has increased due to the availability of more effective therapies such as radiation therapy and chemotherapy to control the extracranial disease [6]. However, the use of radiation therapy poses a high risk of neurocognitive dysfunction among patients with brain metastasis [7]. Some studies show that high precision radiation therapy (radiosurgery and hippocampal avoidance radiotherapy), and the use of memantine can improve retention of neurocognitive function following radiation therapy in patients treated for brain metastasis [8]. Patients with brain metastasis treated with whole brain radiation therapy (WBRT) are more likely to develop impaired neurocognitive function that can affect learning, mem-

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ory, and spatial processing, and lead to dementia [9]. It is estimated that 80% of patients can experience impairment of at least one neurocognitive function within 12 months of receiving WBRT [10]. All forms of radiation therapy including stereotactic radiosurgery (SRS) and hippocampal avoidance whole brain radiotherapy (HA-WBRT) have the potential to affect neurocognitive function [11,12]. Several pharmacological strategies such as peroxisome proliferator activated receptor agonists, renin-angiotensin system blockers, CNS stimulants, donepezil, and glucocorticoids have been tested for their efficacy in preventing neurocognitive impairment after radiation therapy but none have been widely adopted [13]. However, only memantine therapy has been shown to significantly mitigate neurocognitive deterioration induced by radiation [14]. Memantine is a low-affinity voltage-dependent noncompetitive glutaminergic N-methyl D-aspartate receptor (NMDAR) antagonist which favourably binds to the NMDARs and prevents synaptic development [15].

Radiation therapy causes an ischemia-hypoxia cascade which increases glutamate levels and results in the overactivation of NMDA receptors leading to the flooding of calcium ions into cells [16,17]. This leads to cellular imbalance, excitotoxicity, and neuronal cell death. By preferentially binding to NMDARs memantine inhibits the entry of calcium ions into neurons. This prevents the disruption of synaptic plasticity, which could lead to neurocognitive impairment [18]. Despite the fact, that memantine can mitigate neurocognitive deterioration following radiation therapy, a literature search reveals a lack of comprehensive data on memantine efficacy in preventing neurocognitive functions. Therefore, we set out to conduct this comprehensive review to gather data on the efficacy of memantine in preventing neurocognitive dysfunction induced by radiation therapy in patients with brain metastasis.

Materials and methods

Protocol and registration

The recommended reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement [19] was used to create this study protocol, which has been registered at PROSPERO (CRD42021290179).

Data sources

A comprehensive systematic search was performed in five medical electronic databases including PubMed®, Scopus®, Embase®, Cochrane Library Central® and ClinicalTrail.gov.in from their inception to November 2021 using predefined search terms that included brain metastases, brain neoplasm, memantine, NMDA receptor antagonist, radiotherapy, radiation therapy, whole brain radiotherapy, WBRT, stereotactic radiosurgery, SRS, hippocampal avoidance whole brain radiotherapy, HA-WBRT, cognitive function, cognitive dysfunction, spatial processing, memory, recall, delayed recognition and quality of life. The details of search strategies performed in different databases are presented in *Appendix A*. To avoid missing any relevant literature, a comprehensive hand search of references was performed. We reviewed all the studies published in English to assess the impact of memantine in preventing neurocognitive dysfunction in patients with brain metastases who received radiation therapy.

Study selection

The records extracted from the above indicated databases were submitted to Mendeley for duplication removal. The title and abstracts of the retrieved studies were reviewed for study eligibility by two authors independently. The details of inclusion criteria are presented in PICOS format in *Appendix B.* Independently the authors also searched the references of the selected citations to identify missing studies, if any. Any disagreements between authors about the study selection and eligibility were resolved through discussion, and a conclusion was made after all the authors had come to a consensus. Nonhuman studies, nonexperimental studies, studies published in non-English language, surveys, review articles, systematic-review, meta-analysis, abstracts, posters, editorials, seminar presentations, commentaries, notes, and full-text unavailable articles were excluded from this review.

Data extraction

Two authors independently extracted data from all of the included studies and documented it in a uniquely designed data extraction tool (©Microsoft excel-2019). The data includes the study characteristics such as first author name, publication year, country, study design, total sample size, study population in each group (intervention group/control group), number of patients lost the follow-up, age (year), primary tumour site, type of radiation therapy, dose of radiation therapy, intervention provided including for memantine, details of dose, route, frequency of administration and its duration, and for the comparator commonly a standard of care or usual care or placebo, follow-up period in days and the outcomes measured including primary and secondary outcomes. The data extraction sheet in excel was perfected by trial and error, with two articles as pilots.

Data synthesis

The primary outcome was to assess and compare the efficacy of memantine therapy versus standard of care or usual care or placebo in mitigating neurocognitive dysfunction induced by radiation therapy in patients with brain metastases. The secondary outcome was to assess and compare the changes in patients' quality of life (QoL) in patients receiving memantine therapy versus standard of care or usual care or placebo as well as to assess the toxicity of memantine therapy. The decline, concordant and increased indicates the significant reduction, no significant changes, and significant improvement in the outcomes of at least one neurocognitive function test, any domains of QoL and toxicity in the follow-up compared to the baseline.

Risk of bias

The risk of bias (RoB) for the included randomized control trials were assessed using the Cochrane RoB tool by two authors independently. The Cochrane RoB assessment tool includes the domains of randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other bias, with overall results categorising as "low-RoB," "unclear-RoB," and "high-RoB" [20]. The Low-RoB indicates that the presence of bias is unlikely to affect the study's outcomes, whereas the unclear and high-RoB suggest that the presence of bias may raise some doubt and have a significant impact on the study's outcomes, respectively. The final decision on the RoB by two independent authors was transferred into the RevMan-Version 5.3 electronic tool to create images of the RoB graph and RoB summary [21]. Any disagreements during judgment were resolved through discussion among the authors.

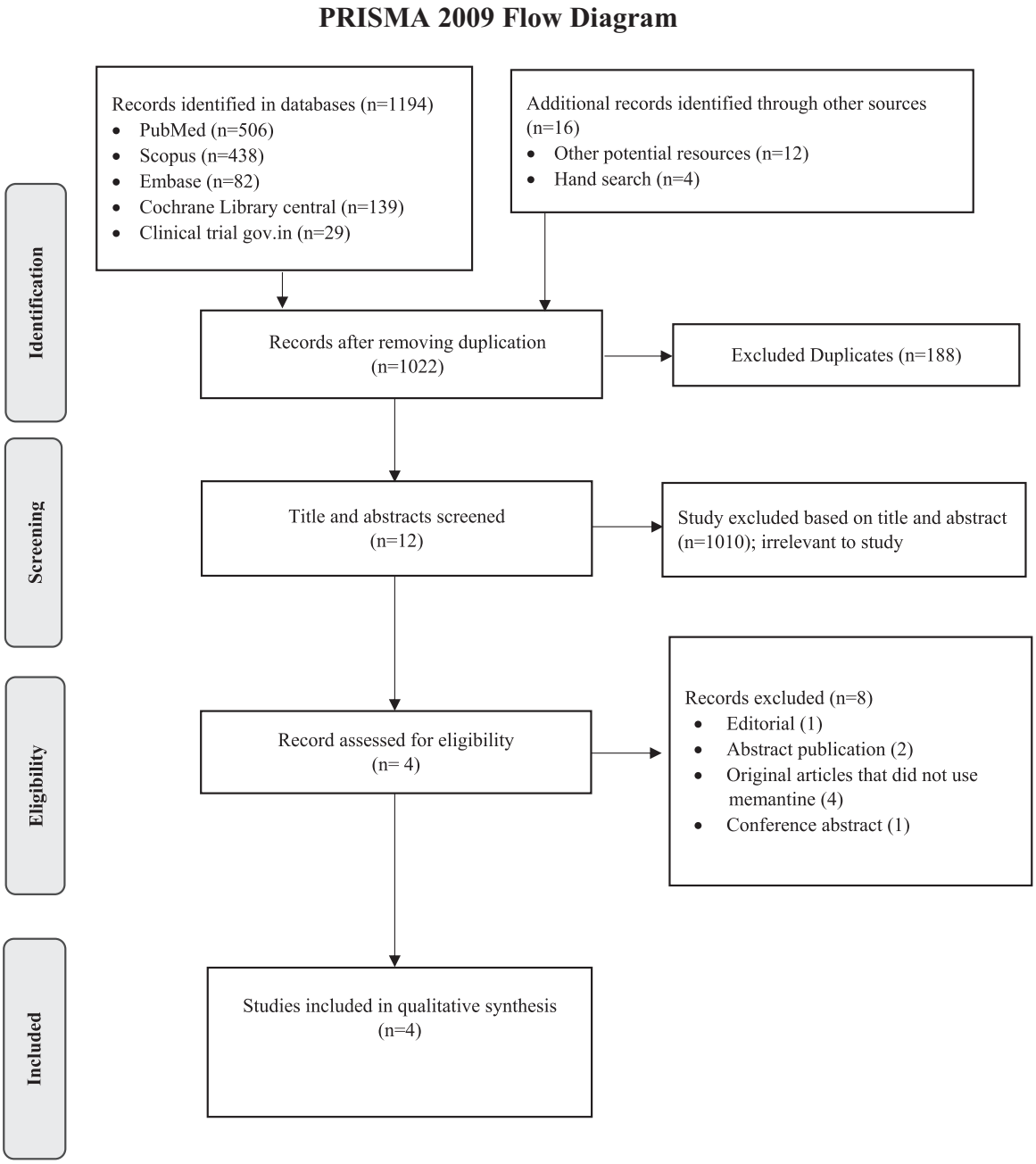


Fig. 1. Flow diagram of study selection process (PRISMA flowchart).

Results

Study selection

A total of 1210 citations were identified through electronic databases and reference searches. The details of the study selection process are presented in the PRISMA flow chart (Fig. 1). After the removal of duplicates (n = 188), 1,022 citations' titles and abstracts were screened. Of them, 1,010 citations were excluded after reviewing title and abstracts that were irrelevant to study inclusion criteria, then editorial (n = 1), abstract publications (n = 3) and full-text articles that did not use memantine therapy (n = 4) were also excluded based on exclusion criteria. The details of excluded studies are presented in *Appendix C.* Finally, four studies that met study inclusion criteria were included for final data synthesis.

Study characteristics

The characteristics of the four selected studies are presented in Table 1. All four studies were conducted in North America - (n = 3, USA and Canada) [22–24] and (n = 1, Canada) [25]. All the selected studies were Randomized Control Trials (RCTs) which were conducted within the period of 2013 to 2020.

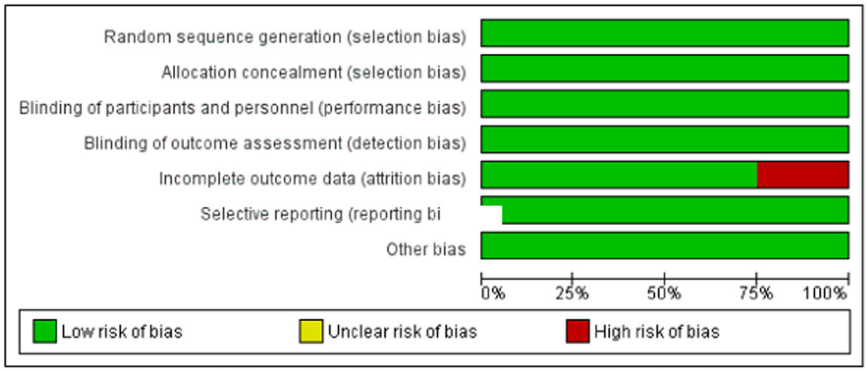
Risk of bias

The Cochrane RoB was used to assess the RoB for the included RCTs. The RoB graph and the summary are presented in Fig. 2. All studies had a low selection bias, performance bias, detection bias, reporting bias and other ROB, whereas, three of the four studies

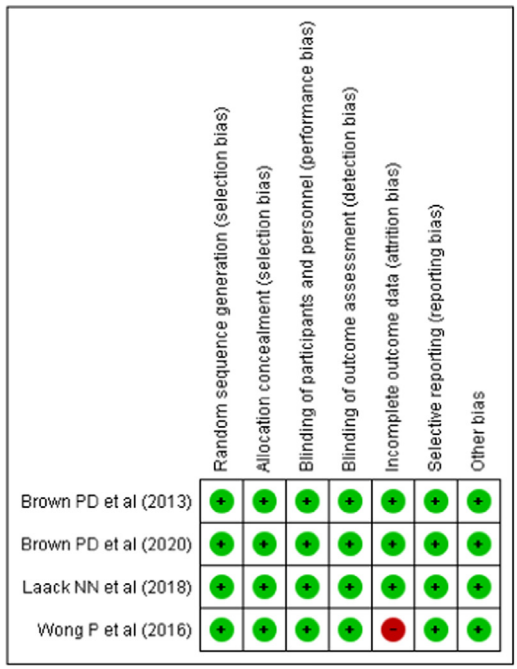
Table 1
Characteristics of selected studies.

• Author • Country • Year	Study design	Total sample size	• Study participants (IG/CG) n/n • Loss of follow-up (IG/CG) n/n	Median age (IQR)]	Primary tumor site	Radiation therapy • Type • Dose • Schedule	Intervention provided (Memantine therapy, dose, frequency, route, and duration)	Comparator (standard care or usual care or placebo)	Follow-up (mo)	Outcome measured (primary and /or secondary outcomes)
• Brown et al[22] • USA/Canada • 2013	• RCT • Double blinded • Multicenter	508	• Study participants (IG/CG) = 256/252 • Loss of follow-up (IG/CG) 0/0 • Study participants (IG/CG) = 7/5 • Loss of follow-up (IG/CG) = 0/2	59 (29–86)	Lung cancer: 355 (69.8%) Breast cancer: 75 (14.7%) Colon cancer: 5 (0.9%) Other cancer: 73 (14.3%)	• WBRT • 37.5 Gy • 15 × 2.5 Gy fractions	Memantine schedule: Wk 1: 5 mg OD, Wk 2: 5 mg BID, Wk 3: 10 mg AM / 5 mg PM, Wk 4–24: 10 mg BID. ***Total duration of therapy:*** 24 wks	Placebo	13	• Cognitive decline • Time to cognitive failure • Overall survival • Progression free survival • Adverse effect
• Wong et al[25] • Canada • 2016	• RCT • Double blinded • Single center	14		64 (34–78)	Lung cancer: 7 (50%) Breast cancer: 4 (28.5%) Melanoma: 1 (7%) Thyroid cancer: 1 (7%) Colon cancer: 1 (7%)	• WBRT: • 37.5 Gy • 15 × 2.5 Gy fractions	Memantine schedule: Wk 1: 5 mg OD, Wk 2: 5 mg BID, Wk 3: 10 mg AM / 5 mg PM, Wks 4–24: 10 mg BID. ***Total duration of therapy:*** 24 wks	Placebo and neither	6	• NAWM • Cognitive function • QoL
• Laack et al[23] • USA/Canada • 2018	• RCT • Double blinded • Multicenter	554	• Study participants (IG/CG) = 205/201 • Loss of follow-up (IG/CG) = 73/75	59 (29–86)	-	• WBRT: • 37.5 Gy • 15 × 2.5 Gy fractions	Memantine schedule: Wk 1: 5 mg OD, Wk 2: 5 mg BID, Wk 3: 10 mg AM / 5 mg PM, Wk 4–24: 10 mg BID. ***Total duration of therapy:*** 24 wks	Placebo	12	• Effectiveness of memantine in preventing cognitive function • QoL on association with cognitive function
• Brown et al[24] • USA/Canada, • 2020[2]	• RCT • Double blinded • Multicenter	518	• Study participants (IG/CG) = 261/257 • Loss of follow-up (IG/CG) = 0/0	61.5 (20–91)	Lung cancer: 307 (57.7%) Bone cancer: 2 (0.3%) Breast cancer: 96 (18.5%) Colon cancer: 10 (5.1%) Gastroesophageal junction cancer: 2 (0.3%) Esophagus cancer: 13 (2.5%) Cancer of Kidney: 13 (2.5%) Ovary cancer: 6 (1.5%) Skin cancer: 22 (4.2%) Anal cancer: 3(.5%) Pancreatic cancer: 2 (0.3%) Other cancer: 42 (8.1%)	• HA-WBRT and WBRT • 30 Gy • 10 × 3 Gy fractions	HA-WBRT + memantine. Memantine schedule: Wk 1: 5 mg OD, Wk 2: 5 mg BID, Wk 3: 10 mg AM / 5 mg PM, Wks 4–24: 10 mg BID. ***Total duration of therapy:*** 24 wks	WBRT + memantine 5 mg OD × 1 wk followed by 5 mg BID × 1 wk, then 10 mg in the morning and 5 mg at night × 1 wk followed by 10 mg BID × 21 wks	6	• Cognitive failure risk • Cognitive decline • Intracranial PFS • OS • Toxicity • QoL

BID = bis in die (twice daily); CG = control group; Gy = gray; HA-WBRT = hippocampal avoidance whole brain radiation therapy; IG = intervention (memantine) group; IQR = inter quartile range; NAWM = normal appearing white matter; OD = once in a day; PO = per os (orally); QoL = quality of life; RCT = randomized controlled trial; WBRT = whole brain radiation therapy; PFS = progression free survival; OS, overall survival.



(a) Risk of Bias Graph presented across all RCTs



(b) Risk of BiasSummarypresented across all RCTs

Fig. 2. Risk of bias graph and summary of all included RCTs.

[22–24] had a low detection bias. Overall, three of the four studies [22–24] had a low ROB and one of the four studies [25] had a high RoB.

Characteristics of study participants

A total of 1,508 participants were enrolled in the four selected studies with 68 participants lost follow-up before study completions. Finally, 1,444 patients with brain metastases who received brain radiation therapy were included in the final analysis (Intervention group [n = 729] and Control group [n = 715]). The median age of study participants was 60.8 (IQR 20–91) years. Participants had diagnoses of lung cancer 669/1440 (46.4%), breast cancer 175/1440 (12.1%), colon cancer 16/1440 (1.1%) and other cancer and/or unknown cancer 580/1440 (40.2%). Details are presented in Table 1.

Radiation therapy provided

All study participants in both groups received WBRT at doses of 30–37.5 Gray in 10–15 fractions to treat their brain metastases (Table 1).

Prescribing pattern and duration of memantine therapy

All patients in the intervention group received memantine therapy at a dose of 5–20 mg for 24 weeks (Table 1).

Outcome measures

For all included studies, the desired outcomes were listed in Table 2. Summary of all included studies are depicted in *Appendix D*. The study outcomes were assessed between baseline visit to end of follow-ups (total duration: 6–13 months). The details of the primary (neurocognitive function) and secondary outcomes (QoL and toxicity) are presented in Table 2.

Neurocognitive function

Three of the four selected studies assessed the impact of memantine therapy in preserving neurocognitive functions [22,24,25]. The assessed neurocognitive functions include recall and recognition, verbal fluency, complex attention, and executive function and overall neurocognitive function. Normal appearing white matter (NAWM) was also assessed.

Table 2
Details of outcomes measured among selected studies.

• Author • Country • Year	Primary outcomes	Assessment tool used	Duration of follow-up (assessment of outcomes)	Primary outcomes related to neurocognitive parameters – first visit to next or end of follow-up	Difference between groups from next or end of follow-up to baseline or first visit	Significance level *(P < .05)*	Overall summary
Primary outcomes							
• Brown et al[22] • USA/Canada, • 2013	Neurocognitive function	HVLT-R	At 2 and 13 mo	HVLT-R, median (IQR) • IG: −0.36 (−1.77 to 0.56) to 0 (−2 to 0.71) • CG: −0.72 (−1.76 to 0) to 0 (−1.82 to 0.72)	Median difference IG: 0.36 CG: 0.72	.39	Although *P*-value not significant for recall and recognition between groups the differences favored the memantine arm
• Wong et al, • Canada • 2016[25]	NAWM	MRI	At 2- and 6-mo visits.	NAWM, AUC • IG: 0.8–0.9 AUC • CG: 1.1–3 AUC	AUC difference IG: 0.1 CG: 1.9	.01	Memantine significantly reduced NAWM AUC changes following radiotherapy.
	Neurocognitive functions	COWAT	At 2-, 4- and 6-mo visits.		-	.03	Patients on memantine retained better cognitive functions than those on placebo.
		MMSE			-	-	Not mentioned.
		HVTL-R			-	.10	Recall and recognition was trending towards improvements in the memantine group.
• Brown et al[24] • USA/Canada • 2020 • NCT02360215	Neurocognitive functions	HVLT-R	At 2 mo and 12 mo visit.	Total recall (mean ± SD) • IG: −0.63 ± 1.25 to −0.55 ± 1.52 • CG: −0.47 ± 1.21 to −0.34 ± 1.34	Mean difference IG: 0.8 CG: 0.13	.058	HA-WBRT plus memantine better preserves delayed recall and recognition.
		TMT-A		TMT-A (mean ± SD) • IG: −1.42 ± 6.27 to −1.28 ± 5.10 • CG: −1.3 ± 5.47 to −0.70 ± 3.10	Mean difference IG: −0.14 CG: −0.75	.59	No significant difference in cognitive deterioration rates between arms.
		TMT-B		TMT-B (mean ± SD) • IG: −2.86 ± 16.60 to −2.49 ± 8.18 • CG: −2.27 ± 9.91 to −1.44 ± 6.59	Mean difference IG: −0.37 CG: −0.83	.92	No significant difference in cognitive deterioration rates between arms at 2 and 12 mo. The HA-WBRT + memantine arm less likely to have deterioration in TMT-B at 4 mo (23.3% *v* 40.4%; *P* = .01.
		COWAT		COWAT, mean ± SD • IG: −0.28 ± 0.96 to −0.44 ± 1.71 • CG: −0.29 ± 1.04 to −0.21 ± 1.65	Mean difference IG: 0.16 CG: −0.08	<.0001	Statistically significant difference in verbal fluency from 2 mo to 12 mo.

(*continued on next page*)

Table 2
(*continued*)

• Author • Country • Year • Clintrials #	Secondary outcomes	Assessment tool used	Duration of follow-ups (Assessment outcomes)	Secondary outcomes related to quality of life and/or toxicity profile. (Baseline or first visit to next or end of follow-up)	Difference between groups from next or end of follow-up to baseline or first visit	Significance level *(P < .05)*	Overall summary
• Laack et al[23] • USA/Canada • 2018 • NCT00566852	Quality of life	FACT-Br score	At 6 mo of follow-up.	FACR –Br score, median (IQR) • IG: 0 (−14 to 16) at 6 mo • CG: 1 (−10 to 12) at 6 mo	-	*.77*	No statistical difference was observed between the memantine and placebo arms.
• Brown et al[24] • USA/Canada • 2020 • NCT02360215	Patient's quality of life	MDASI-BT symptoms severity score	At 2 and 12 mo.	MDASI- BT score (symptoms severity, mean ± SD) • IG: 0.48 ± 1.39 to 0.53 ± 1.69 • CG: 0.61 ± 1.62 to 0.09 ± 1.47	Mean difference IG: −0.05 CG: 0.52	*.57*	Symptom severity changes was lower in interventional arm (HA-WBRT plus memantine) with longer follow-up.
		MDASI-BT interference score		MDASI- BT score (interference score, mean ± SD) • IG: 0.84 ± 2.45 to 0.64 ± 2.86 • CG: 1.09 ± 2.79 to 0.14 ± 3.00	Mean difference IG: 0.2 CG: 0.95	*.91*	Symptom interference, cognitive factor, and neurologic factor did not show any significant treatment effects.
		MDASI-BT cognitive factor score		MDASI- BT score (cognitive factor, mean ± SD) • IG: 0.45 ± 1.81 to 1.04 ± 2.33 • CG: 0.50 ± 1.95 to 0.50 ± 1.69	Mean difference IG: −0.59 CG: 0	*.19*	
		MDASI-BT Neurologic factor score		MDASI- BT score (neurologic factor, mean ± SD) • IG: 0.17 ± 1.91 to 0.60 ± 2.20 • CG: 0.28 ± 2.31 to 0.40 ± 2.53	Mean difference IG: −0.43 CG: −0.12	*.88*	
		EQ5D5L index score		EQ5D5L score (mean ± SD) • IG: −0.04 ± 0.17 to −0.03 ± 0.17 • CG: −0.05 ± 0.16 to −0.01 ± 0.14	Mean difference IG: −0.01 CG: −0.04	Between IG/CG at 2 mo: *.86* Between IG/CG at 12 mo: *.92*	No differences were seen between study arms at baseline or over time for the EQ-5D-5L.
• Brown et al[22] • USA/Canada • 2013 • NCT00566852	Toxicity profile	CTCAE V3.0	At 13 mo of follow-up.	Number of patients with adverse events, n (%) • IG:80 (31.87%)CG:67 (27.24%)	-	Not reported	No statistically significant differences between the treatment arms.
• Brown et al[24] • USA/Canada • 2020 • NCT02360215	Toxicity profile	CTCAE V4.0	At 12 mo of follow-up.	Number of patients with adverse events, n (%) • IG: 98 (42.24%) • CG: 106 (47.75%)	-	Not reported	No statistically significant differences between the treatment arms.

AUC = area under curve; CG = control group; COWAT = controlled oral word association test; CTCAE = common terminology criteria for adverse events; FACT-Br = functional assessment of cancer therapy-brain; HA-WBRT = hippocampal avoidance whole brain radiation therapy; HVLT-R = Hopkins verbal learning test-revised; IG = interventional group; IQR = inter quartile range; MDASI-BT = MD Anderson symptom inventory brain tumor; MMSE = mini mental state examination; MRI = magnetic resonance imaging; NAWM = normal appearing white matter; SD = standard deviation; TMT-A = trail making test-part A; TMT-B = trail making test part-B; WBRT = whole brain radiation therapy.

Table 3
Details of ongoing randomized control trials assessing neurocognitive outcomes with memantine for brain metastatic patients.

Clinical trial number and phase of study	Title	Intervention group	Control group	Expected primary outcomes of the study. (Expected time frame for study completion)
NCT03550391 Phase 3	Stereotactic radiosurgery compared with hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine for 5–15 brain metastases.	WBRT 30 Gy in 10 fractions + memantine	SRS 18–20 or 22 Gy in single fraction.	• Overall survival: SRS versus HA-WBRT + memantine therapy • Neurocognitive progression-free survival: SRS versus HA-WBRT + memantine (Time frame: 4.5 yr)
NCT04801342 Phase 2	Neurocognitive outcome of bilateral or unilateral hippocampal avoidance WBRT with memantine for brain metastases.	Unilateral hippocampal avoidance wbrt with memantine	Bilateral HA-WBRT + memantine.	• HVLT-R memory score (Time Frame: at 6 mo after WBRT)
NCT05013892 Phase 2	NTS WBRT VS HA WBRT in brain metastases.	NTS-WBRT + memantine	HA-WBRT + memantine.	• Patient reported quality of life: NTS-WBRT versus HA-WBRT • Symptom burden: NTS-WBRT versus HA-WBRT (Time frame: 4 mo)
NCT05045950 Phase 2	Optimizing neurocognition with whole brain radiation therapy (WBRT) using upfront pulsed reduced dose-rate (PRDR) technique.	WBRT-PRDR + memantine.	Historical controls.	• Impact of PRDR WBRT on neurocognitive decline (COWAT, HVLT-R, TMT-A, TMT-B) (Time frame: 4 mo)
NCT04804644 Phase 3	Testing if high dose radiation only to the sites of brain cancer compared to whole brain radiation that avoids the hippocampus is better at preventing loss of memory and thinking ability.	SRS	HA-WBRT QD for 2 wk + memantine PO QD or BID for up to 24 wk.	• Time to neurocognitive failure (Time frame: 1 yr)
NCT04588246 Phase 3	Testing the addition of whole brain radiotherapy using a technique that avoids the hippocampus to stereotactic radiosurgery in people with cancer that has spread to the brain and come back in other areas of the brain after earlier stereotactic radiosurgery .	HA-WBRT + salvage SRS + memantine PO QD or BID for 24 wk.	Salvage SRS.	• Time to Neurologic Death (Time frame: up to 3 yr)
NCT04567251 Phase 3	Survivorship study of cancer patients who receive cranial radiation therapy.	Memantine hydrochloride + donepezil hydrochloride for 17 wk	Placebo.	• Effect of memantine hydrochloride + donepezil hydrochloride on cognition • Feasibility of using a digital symptom tracking application on HRQoL and cognition

BID = bis in die (twice daily); COWAT = controlled oral word association test; Gy = Gray; HA-WBRT = hippocampal avoidance whole brain radiation therapy; HRQoL = health related quality of life; HVLT-R = Hopkins verbal leaning test-revised; NTS WBRT = normal tissue sparing whole brain radiation therapy; PO = per os (oral administration); PRDR = pulsed reduced dose-rate; QD = quaque die (once a day); SRS = stereotactic radiosurgery; TMT-A = trail making test-part A; TMT-B = trail making test part-B; WBRT = whole brain radiation therapy.

Recall and recognition – Three studies assessed the impact of memantine therapy on recall and recognition using the Hopkins Verbal Learning Test-Revised (HVLT-R) scale. Two studies reported a decline in the HVLT-R score indicating that recall and recognition was improved in the interventional (memantine) group as compared to the control group at 2–13 months of follow-up. However, the differences between both groups were not statistically significant ($P = .39$ and .10) [22,25]. A third study reported that recall and recognition were improved in the group receiving memantine therapy compared to the control group but the difference between groups was of statistically borderline significance ($P = .05$) [24].

Verbal fluency – Two studies performed the controlled oral word association test (COWAT) to assess verbal fluency and found a statistically significant improvement in the memantine therapy group compared to the control group ($P = .03$ and $P < .0001$) [24,25].

Complex attention and executive function – One study [24]. evaluated the cognitive deterioration rate (attention and executive function) using trail making test part A (TMT- A) and trail making test part B (TMT-B) in both groups. There was no significant difference in cognitive deterioration rates in the memantine therapy group compared to the control group at 2 months to 12 months. However, with the administration of WBRT cognitive deterioration at 4 months was less likely with memantine therapy (23.3% *v* 40.4%), and this was statistically significant ($P = .01$) [24].

Overall neurocognitive function – Among the four studies, one assessed overall neurocognitive function using mini-mental state examination (MMSE) but have yet to report the results [25].

Normal appearing white matter – One study used magnetic resonance imaging (MRI) to estimate the change in the degree of NAWM according to the area under the curve (AUC) and found lesser changes in AUC in the memantine therapy group compared

to the control group, which was statistically significant ($P = .01$) [25].

Quality of life

Out of four selected studies, two studies assess the patient's QoL comparing the intervention and control groups [23,24]. One study assessed the patient's QoL using the functional assessment of cancer therapy-brain (Fact-Br) questionnaire. At 6 months follow-up there was no significant improvement in the patient's QoL in the intervention group compared to the control group [23]. A separate study reported the QoL using the MD Anderson Symptom Inventory Brain Tumour (MDASI-BT) and EQ5D-5L index. The core assessment of symptom severity using the MDASI-BT score showed improvement in symptom severity in the intervention group (HA WBRT plus memantine) compared to the control group (WBRT plus memantine), which was statistically significant. However, the MDASI-BT interference score, MDASI-BT cognitive factor, MDASI-BT neurological factor and EQ5D5L scores were not statistically significant at 12 months compared to 2 months in both groups [24].

Toxicity

The toxicity profile of memantine therapy compared to placebo was assessed into two of the selected studies [22,24]. In both studies, similar frequency and types of toxicity was observed, which was statistically nonsignificant. The most commonly observed toxicities were grade 3–4 fatigue, alopecia, nausea, and headache [22]. (Table 2)

Ongoing clinical trials

A total of seven ongoing clinical trials (NCT03550391, NCT04801342, NCT05013892, NCT05045950, NCT04804644, NCT04588246, NCT04567251) were identified that aim to assess the impact of memantine therapy in the prevention of neurocognitive dysfunctions among the patients who will be receiving radiation therapy for brain metastases. Of these seven, three studies are phase II and four studies are phase III, with four of the seven being conducted in a single center and three multi-institutional RCTs. The expected time frame for the completion of these ongoing trials ranges between 2022 and 2030. The details of ongoing clinical trials are presented in Table 3.

Discussion

We present a systematic review evaluating the efficacy of memantine in preserving neurocognitive functions in patients with brain metastases receiving radiation therapy. This systematic review was executed by following the comprehensive review approaches to feature the potential benefits and efficacy of memantine in mitigating neurological impairment induced by radiation therapy. Our search identfied four studies conducted on this topic, all in North America, mostly due to the lesser acceptance rate and utilization of memantine in patients with brain metastases due to the lack of comprehensive data on this [26].

We identified four studies relevant for this systematic review, with clinical improvement in neurocognitive function following memantine therapy when compared to a control groupt in three studies [22,24,25]. However, given the high level of heterogenicity in tools used for assessing outcomes a meta-analysis was not possible [27]. Several of the primary and secondary outcomes of our review had clinical improvement favouring the memantine arm. In all studies, memantine was initiated within 3 days of WBRT and was continued for 6 months with gradual dose escalation from 5 mg to 20 mg per day. We note neuronal damage starts during the initial days of radiation therapy and may cause cognitive impairment. Hence, memantine should be started along with radiation therapy [28]. An earlier trial among the four selected studies, demonstrated a neuroprotective effect of memantine and reported, the HVLT-R score was less at 13 months when comparing the memantine arm against the control arm, yet no statistical difference was found [22]. Although the study reported a borderline significant reduction in delayed recall at 6 months ($P = .059$) [22], this could have occurred as a result of the large number of participants lost during follow-up [29,30]. This study would provide strong evidence of memantine as a neuroprotective agent in patients receiving WBRT plus memantine with a clinically meaningful result. A recent study reported memantine administered with HA-WBRT resulted in a significant improvement in neurocognitive decline of 26% with an improvement in patients' symptom profiles [24]. A separate study assessed the neuroprotective effect of memantine by comparing the vascular changes using MRI and noted memantine significantly reduced the vascular changes after radiation therapy [25]. Among two studies assessed for QoL, one reported a reduction in the symptoms severity score favouring memantine as a neuroprotective agent and found it to be statistically significant [24]. However, a separate study did not find any changes in QoL score in participants receiving memantine when compared to those receiving a control therapy [23]. In all studies that assessed the toxic profile of intervention, the reported memantine toxicities were indistinguishable when compared with those of the control group [22,24].

The major limitation of the study was the heterogeny in extracted data (tools used in outcome assessment and sample size), thereby restricting our choice of meta-analysis. Reporting bias assessed to be present in one study, also impacted study results.

Conclusion

Based on the results available for this review, memantine appears to have some neuroprotective effect with no increase in toxicity in patients with brain metastases who receive radiation therapy. Memantine is reasonable to consider during WBRT to prevent long-term cognitive failure. To date there is no credible data available for recommending memantine in patients receiving SRS or hippocampal avoidance RT treatment. Ironically, SRS or HA-WBRT is at present the standard of care in patients expected to survive for a longer period (presumably 12 months) where neurocognitive function preservation is critical. Hence, it is imperative to assess the impact, if any, of memantine with SRS or HA-WBRT in prospective studies. It is necessary to conduct more controlled research in different patient cohorts with different QoL measures. Such research could in turn inform guidelines to standardize the use of memantine to prevent radiation induced neurocognitive dysfunction in patients with brain metastases.

Declaration of Competing Interest

Authors of this manuscript declares that there is no conflict of interest associated with this paper.

CRediT authorship contribution statement

Haripriya Parapparambil Surendran: Conceptualization, Project administration, Methodology, Investigation, Data curation, Writing – original draft. **Sujit Kumar Sah:** Project administration, Methodology, Data curation, Formal analysis, Writing – original draft. **Dhanya Mary Louis:** Methodology, Investigation, Data curation, Writing – original draft. **Sruthi Kalavagunta:** Validation,

Writing – original draft. **Narmadha Mukunthu Poornachary:** Writing – review & editing. **Selin Chiriyankandath Joy:** Writing – review & editing. **Debnarayan Dutta:** Conceptualization, Methodology, Writing – original draft, Supervision.

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Ethical approval

In this systematic review, previously published data was used for the synthesis of data. Therefore, provision for ethical approval and informed consent was not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminoncol.2023.09.004.

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Preservation of cognitive function after brain irradiation

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Abstract

Objective: Approximately 50–90% of brain metastatic patients who receive radiation therapy (RT) exhibit cognitive decline which may affects the quality of life of cancer survivors. Hence preservation of cognitive functions in brain metastatic patients becomes important. This review aims to evaluates the pathology or mechanism of cognitive function impairment after brain irradiation and strategies available to preserve cognitive function after radiation therapy.

Data Sources: Published articles evaluating the pathology behind radiation induced cognitive impairment and strategies to resolve or preserve cognitive impairment were searched for in scientific databases (eg: PubMed, Scopus, Cochrane database, Google scholar) using keywords including memantine, brain metastases, radiation therapy, pathophysiology, pathogenesis, mechanism and prevention

Data Summary: Several hypotheses have been offered to explain the mechanism of radiation induced cognitive decline. Among them, vascular hypotheses play a significant role. Some pharmacological agents have been also tested in patients receiving radiotherapy, memantine was found beneficial based with the reference to existing data.

Conclusion: Future studies are required to evaluate the impact of memantine in different types of radiation therapy procedures and its effects on quality of life of brain metastatic survivors.

Keywords

Memantine, whole brain RT, HA-WBRT, WBRT, SRS, radiosurgery, cognitive function, impairment

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Introduction

Brain metastasis (BM) occurs in ten to thirty percent of adults and six to ten percent of children with systemic malignancies.[1,2] Because of refined/advanced (systemic) cancer treatments that prolong life and allow BM to develop, the incidence of BM is on the rise. Advances in imaging techniques (MRI or -CT) also contribute in the early detection of BMs.[3] Brain metastasis occurs in varying proportions with different types of cancers viz 15–20% breast cancer, 36–64% lung cancer and 5–20% with skin cancer.[4]

Metastatic cascade is a series of events and complex mechanisms (genetic, epigenetic, and biochemical modifications in tumour cells) that lead to metastatic spread from primary tumour. Detachment from the initial location causes invasion and intravasation into tissues and blood vessels, ending in hematogenous dissemination, arrest in brain capillaries and extravasation.[5] To encourage angiogenesis and proliferation in response to local growth stimuli (niche), cancer cells must eventually invade the surrounding tissue.[6] The colonizing cells search out for microenvironments which are favourable for their growth and development and then produce micro metastases that can spread to other cells.[7]

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The Blood Brain Barrier (BBB) is a structural and functional barrier that regulates the brain microenvironment. Tumour cells can bypass this barrier and establish metastatic colonisation by adapting various cell-cell adhesion proteins (cyclo-oxygenase 2, heparin binding epidermal growth factor, and alpha-2,6 sialyltransferase) to metastatic tumours. When tumour cells adhere to the BBB, infiltrative and transmigratory processes allow the BBB to open. The inflammatory brain milieu is later used by tumour cells as a growth factor (niche).[8]

BMs are symptomatic in sixty–seventy percent of patients with neurologic symptoms such as speech difficulty, visual and hearing problems (focal neurological deficits-forty percent), headache (forty-five percent), and seizures (fifteen to twenty percent). Mental status and cognition may be affected in patients with numerous metastases and/or excessive intracranial pressure (IP).

Brain imaging (MRI and CT) plays a critical role in the diagnosis of BMs in both symptomatic and asymptomatic individuals, as well as in patient management. Intracranial bleeding, herniation, mass effect, and hydrocephalus can all be seen with computed tomography (CT). For lesions in the posterior fossa or many punctate metastases, MRI with intravenous contrast is preferable over CT because of its higher sensitivity.[9]

Role of radiation therapy

The primary approaches to the treatment of brain metastasis include surgery and WBRT. In WBRT, the entire brain and the brain stem are irradiated. With the improvement of technologies, new approaches like Intensity modulated radiotherapy, stereotactic radiosurgery (SRS), hippocampal avoidance – whole brain radiotherapy (HA-WBRT) can be used to mitigate the normal tissue damage.[10] SRS uses precise 3D imaging and localization to deliver ablative doses of radiation to the tumour while minimizing the amount of radiation that reaches healthy brain tissue. Radiation to the hippocampal region of the brain has a major contribution in radiation induced cognitive dysfunction. Limiting radiation dose to the bilateral hippocampus can prevent the WBRT associated cognitive toxicity, which is the principle underlying HA- WBRT.[11]

Challenges and concerns related to brain irradiation

Typically, there are three adverse effects (Acute, early delayed/subacute, and late-delayed effects) associated with cranial radiation. Commonly experienced side effects during or shortly after radiation therapy are drowsiness, headaches, nausea, emesis, and worsening of pre-existing localised symptoms. Early-delayed/subacute effects include headache, somnolence, fatigability, and worsening of pre-existing impairments, which is usually recognised 1–6 months after RT, is reversible, and is assumed to be due to demyelination of neurons. Cognitive decline, the worst and most concerned adverse effect after radiation develops after six months and is usually permanent and progressive.[12]

Around 50 to 90 percent of people who receive whole brain irradiation experience cognitive deterioration that is directly associated to the treatment,[13] while about 52 percent of SRS patients experience cognitive deterioration.[14] Cognitive decline may take months to years to manifest after irradiation, and it may worsen with time. Intensity modulated radiation (IMRT), SRS/ SRT, and HA- WBRT are examples of technological advancements that can reduce normal tissue damage. However, after any sort of radiation therapy, neurocognitive impairments such as learning, memory, spatial processing, and dementia still persist.[15]

Possible mechanisms of radiation induced cognitive dysfunction

Multiple cell types in the brain, including astrocytes, endothelial cells, microglia, neurons, and oligodendrocytes, interact dynamically in radiation-induced cognitive deterioration.[15] Irradiation of the brain can result in a decrease in oligodendrocytes and other glial cells, vascular damage, reduced hippocampus neurogenesis, altered adult neuron function, and neuroinflammation due to activated microglia. All of these changes are thought to play a role in the development of radiation-induced cognitive impairment. The deterioration in hippocampus-related processes, such as learning, memory, and spatial information processing, is hypothesized to be caused by radiation-induced reduction of brain stem/precursor cells, particularly in the sub granular zone (SGZ) of the hippocampus dentate gyrus.[14] To explain the mechanism of radiation-induced cognitive impairment, several hypotheses like neuroinflammation, Hippocampal neurogenesis and vascular hypothesis have been offered. Among them vascular damage plays a significant role[16] (Table 1).

Vascular hypothesis

Radiation to brain damages the small vessels and causes small vessel disease and produces symptoms as that of vascular dementia.[17] Vascular insufficiency and infarction in brain tissue are caused by accelerated atherosclerosis and mineralizing microangiopathy, resulting in damage and inflammation. After radiation, electron imaging of the brain microvasculature reveals alterations in the BBB. When the BBB breaks down, leukocytes can enter the brain parenchyma, causing neuroinflammation and a reduction in neurogenesis. The loss of endothelial cells begins

Table 1. Mechanisms of radiation induced cognitive function impairment.

Type	Mechanism	Receptor	Inference
Inflammation	Damages to astrocytes because of RT, leads to the production of proinflammatory cytokines. In order to maintain the homeostasis after RT, microglia get activated and that also leads to the production of proinflammatory cytokines.	Pro inflammatory cytokines (ICAM-1, TNF-a, IL1b, IL-6, Cox-2)	Production of the proinflammatory cytokines by activated astrocytes and microglia lead to inhibition of neurogenesis and cognitive dysfunction.
Hippocampal Neurogenesis	Microglial inflammation induced by RT lead to the disruption of neurogenesis in the dentate gyrus of the hippocampus and the subventricular zone (SVZ).	Dentate gyrus of hippocampus and SVZ	Reduction of dentate gyrus neurogenesis leads to the impairment in normal memory function and encoding new memories.
Vascular Phenomenon	Vascular insufficiency induced by RT results in vascular ischemia leading to significant rise in the level of extracellular glutamate and excessive NMDA activation causing excitotoxicity.	NMDA	NMDA is an iron channel protein and has a role in maintaining synaptic plasticity. Excessive NMDA activation leads to the influx of calcium resulting in cellular disequilibrium and cell death, attributed to cognitive dysfunction.

during RT and lasts for several months. Due to endothelial cell death, remaining blood components such as platelets adhere to the exposed matrix, to form clots. Ischemia occurs when the blood flow to the brain is reduced, followed by necrosis of the brain tissue.[12] Extracellular glutamate levels rise as a result of cranial ischemia caused by vascular insufficiency. In cortical and hippocampal neurons, glutamate is the primary excitatory amino acid neurotransmitter. The N Methyl D Aspartate (NMDA) receptor meant for learning and memory needs glutamate for its activation and glutamate is the neurotransmitter of cortical and hippocampal neurons.[18] Ischemia caused by vascular insufficiency can enhance excitotoxicity through excessive NMDA activation and leads to the emergence of cognitive decline.[19]

Radiation-induced cognitive damage is becoming more well recognised as a complex issue involving many different mechanisms. The inflammatory response commences from the time of radiation and exists after radiation resulting in prolonged tissue demyelination and remodelling. Though deformation takes place in small vessels of the brain soon after RT, it becomes clinically evident only after months or years.[13]

Treatment of cognitive dysfunction

Radiation-related cognitive dysfunction is similar to other types of dementia, such as dementia caused by ageing, dementia caused by stroke, and dementia caused by Alzheimer's disease, and it was predicted that treatments used in these situations could help to ameliorate symptoms in a similar way (Table 2).

Behavioural & reinforcement methods

Behavioural. Being physically active is well known to decrease in cognitive impairment, and exercise may help to more effectively alleviate symptoms. In an animal study where mice were given RT to induce cognitive impairment, 50% of the animals with full brain irradiation were allowed to move on a running wheel for one month following their RT. They discovered that mice who ran on the wheel every day had better spatial memory recall and exerted healing effect on the dentate gyrus neurons of the hippocampus. Despite the fact that the benefits of physical activity on people have yet to be researched, these data suggest that exercise could be employed as an important non pharmacological option for patients undergoing RT for a better quality of life.[20]

While meditation safeguards holistic health, it has shown improvement in cognitive function in cancer patients who have received treatment. Meditation protects people from the damaging effects of stress and emotional imbalance, stabilises the self-identity, strengthens the immune system, helps to attain a peaceful mind and good sleep. Thereby meditation is bound to offer protection and safeguard the cognitive function from RT and improve cognition.[21,22]

Pharmacological methods. Some pharmacological agents (Peroxisome Proliferator Activated Receptor Agents, Renin- angiotensin system blocker, CNS stimulant) have been tested to find out their effectiveness in preventing cognitive impairment. All these agents have shown a recovery from radiation induced cognitive failure. However, they have not been studied in humans.

Table 2. Methods for preserving cognitive function after radiation therapy.

Methods	Mechanism of action	Studies	Results	Remarks
Behavioural methods				
Bio behaviour	Meditation practice provides mental training within the domains of neurocognition and sense of self, regulation of immune system, stress reduction and improved sleep quality	Moss AS et al.[22]	Effect of an 8-week long meditation program showed an improvement in mood, anxiety, tension, and fatigue.	Considerable strategy to preserve neuro- cognitive functions.
Retraining and reinforcement	Physical activity increases the vascularization- oxygen and glucose to the brain- augmenting brain activity.	Wong et al.[20]	Mouse ran on the treadmill daily had better spatial memory retention and partial restoration of new-born neurons in the dentate gyrus of the hippocampus	No studies have been prospectively evaluated in humans
Radiation modification				
Stereotactic radiosurgery (SRS)	SRS can avoid the white matter changes followed by radiation therapy and protects hippocampal stem cell compartment from radiation	NCCTGN0574 Brown et al.[27]	Rate of cognitive deterioration was lower with SRS (64%) than SRS plus WBRT (92%) at 3 months.	Initial treatment with SRS and close monitoring is recommended in newly diagnosed brain metastatic patients.
HA WBRT	By using IMRT (Intensity modulated radiotherapy) Hippocampal dentate gyrus can be avoided to prevent the microglial inflammation.	Yang et al.[26]	HAWBRT- 7% decline in cognitive function WBRT- 30% decline in cognitive function	HA- WBRT was associated with highly promising preservation of memory and quality of life.
Pharmaceutical Method				
PPAR agonist	Role in modulation of inflammation	Zhao W et al.[37,38]	Pioglitazone and Fenofibrate are have been shown to prevent cognitive impairment in rats	No human data
ACE/ ARB	RAS involved in the activation of pro inflammatory cytokines that may play a role in cognitive dysfunction	Lee T C et al.[39]	Rat experiments have shown benefit to RAS blockade in the treatment of radiation induced cognitive impairment.	No human studies
Methylphenidate (MPH)	Dopamine or nor adrenaline reuptake inhibitor	Butler and Meyers[40,41]	Controversial result	Results are not conclusive
Donepezil	Acetylcholine esterase inhibitor	Wartena R et al.[10]	No significant effect	No significant role
Glucocorticoids	Reduces the vasogenic oedema thereby minimizing the cognitive abnormalities induced by tumour oedema	Dinkel K et al.[23]	Showed improvement in cognition	By considering the possible toxicities, they are not considered.
NSAIDS	Anti-inflammatory action	Raber J et al.[42]	Indomethacin reduces 35% of decrease in activated microglia in rats	Human studies are limited
Armodafinil	CNS stimulant	Shaw EG[28]	Results were borderline significant	Future studies needed
Memantine	NMDA receptor antagonist	Brown PD et al.[16]	Memantine on preventing cognitive functions in WBRT showed a borderline significant result.	Now, survival of brain metastases patients improved with treatment advancements, future studies are needed to confirm the result.

(continued)

Table 2. Continued.

Methods	Mechanism of action	Studies	Results	Remarks
		Wong et al.[42]	Memantine significantly reduced normal appearing vascular permeability changes following RT	Considerable strategy to preserve cognitive function following RT.
		Brown PD et al.[26]	Cognitive failure risk was significantly better in the Memantine + HA-WBRT arm than in WBRT + memantine arm	Effective strategy in preserving cognitive function.

Studies with clinical information

Donepezil. Donepezil is a reversible AChE inhibitor that has been approved to treat Alzheimer's disease. Donepezil was found to preserve particular cognitive domains while having no effect on overall cognition.[10]

Glucocorticoids. In patients with brain tumours, glucocorticoids are frequently used to reduce vasogenic oedema. Treatment of vasogenic oedema can minimise the cognitive abnormalities caused by tumour oedema for a short time. They are not used to treat chronic or treatment-related cognitive impairment because of its possible toxicities.[23]

Prevention of cognitive dysfunction

Non-Pharmacological strategies

To avoid and mitigate the damage caused by brain irradiation, a number of non-pharmacological therapies have been developed. Controlling comorbidities including hypertension and diabetes,[24] restricting alcohol consumption, and smoking cessation are some of the most popular therapies used to avoid cognitive decline. Radiation doses to specific parts of the brain (Hippocampus and supratentorial brain) are also used in order to prevent neurocognitive deterioration.[25,26] In an RCT done by Brown et al. in 213 patients with 1 to 3 brain metastases, it was seen that the use of SRS alone as compared to SRS with WBRT resulted in less cognitive deterioration at 3 months (63.5% vs. 91.7%) without any difference in overall survival.[27]

Pharmacological strategies

Several pharmacological strategies have been tested for their efficacy in preventing cognitive impairment, and some strategies have proved to protect brain tissues from the harmful effects of brain irradiation; Nevertheless, with the exception of memantine, no other drugs have shown to prevent radiation-induced neurocognitive decline.

Memantine is a low affinity voltage dependent non-competitive glutaminergic NMDAR antagonist and it preferentially binds to NMDARs, which are ion channel proteins that play a key role in synaptic development (significant mechanism for memory and learning). Radiation Therapy causes an ischemic-hypoxia cascade, which causes glutamate levels to rise, resulting in overactivation of NMDA receptors. Overactivation of NMDA receptors leads to calcium ions flooding inside the cell causing cellular disequilibrium, excitotoxicity, and cell death. Memantine binds to NMDARs preferentially and inhibits calcium ions from entering the cell, preventing synaptic plasticity from being disrupted, which otherwise could lead to cognitive impairment.

The efficiency of memantine in patients getting whole brain irradiation has been studied in a number of trials. Memantine increases neurocognitive preservation among patients treated with WBRT, according to the RTOG 0614 trial published in 2013. Although the p-value for the primary endpoint of delayed recall at 24 weeks was borderline significant ($p = 0.059$), the study's power was likely hampered by the substantial loss to follow-up in this cohort and could be because of short survival period, which is a recurrent concern in research including patients with brain metastases.[16] The National Cancer Comprehensive Network's (NCCN) consensus guidelines now include the use of memantine with WBRT as a result of the RTOG 0614 trial.

Hippocampal Avoidance- Whole brain irradiation and memantine resulted in a relative reduction of 26 percent in neurocognitive deterioration in the NRG- CC001 RCT.[26] There have been no clinical trials to evaluate the efficacy of memantine in patients undergoing stereotactic radiosurgery.

Memantine is available as oral tablets of 5 mg and 10 mg. It has 100 percent bioavailability; therefore, it can be taken with or without food.[28] For adult patients with brain metastases who received WBRT, a regular dose of memantine 20 mg/day, starting 3 days after radiotherapy and lasting up to 24 weeks is recommended.[16]

Memantine is partially metabolized in the liver and excreted by the kidney. In patients with renal or hepatic impairment, dose adjustments are required and daily

doses should not exceed 10 mg in individuals with severe renal impairment. Dizziness, headache, disorientation, diarrhoea, and constipation are all typical adverse effects. Cimetidine, ranitidine, procainamide, quinidine, quinine, and nicotine are found to interact with memantine.[29]

It has been established that synaptic modifications include proliferation and enhanced excitatory activity during the initial days of radiation, followed by synaptic degeneration is the aetiology of cognitive impairment. Prevention of these excitotoxicity is the prompting factor for prescribing memantine.[16]

NCCN guidelines indicate considering memantine in WBRT patients with good prognosis. However, acceptance of memantine is low even in advanced radiation oncology facilities. Poor compliance and acceptance of memantine in brain metastasis are due to various social and cultural reasons. Traditional feeling of nihilism regarding brain metastases and anticipated short survival is the major reason for non-compliance. Even in prospective clinical trial only 29% of patients completed the planned 24-weeks of memantine. Brain metastasis patients have short life span, and quality of life is critical.[30] Memantine may cause nausea, vomiting in a small proportion of patients, and the anticipated side-effect may hinder its usage.[31,32] Memantine preserves cognitive function after radiation therapy. There is an assumption that majority of the patients do not live long enough to avail the small but definitive benefit of memantine. But the fact is that oligo brain metastasis patients with good prognosis (good performance status, thyroid, melanoma, renal origin, small volume disease), almost 20% of the patients have more than 2-year survival.[33–36] Availability and cost of memantine is also a concern. Though cost may not be a concern even in developing countries, availability is a real concern. 'Low cost' of medicine and less number of indications have reduced enthusiasm among the manufacturers. Memantine is often considered an 'orphan' drug. However, with the invent of more potent systemic therapies and increased expectations even after brain metastasis, memantine is receiving renewed interest

Conclusion

Memantine in patients receiving HA-WBRT has a definitive benefit demonstrated with randomized clinical trials. There are a few well designed, appropriately powered and executed clinical trials that have proven benefit of memantine both with WBRT and HA-WBRT. In recent years, there is emergence of innovative treatment techniques for brain metastasis patients such as SRS and HA-WBRT. There is a potential for improvement in survival functions as well. Hence, there is a need for further research regarding the effectiveness of memantine in preventing cognitive damage after brain irradiation. Future research should focus on evaluating the impact memantine in various types of radiation therapy procedures, as well as the quality of life of patients who get memantine in addition to standard care.

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