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CRITICAL REVIEW

Radiation Therapy in Alzheimer's Disease: A Systematic Review

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Purpose: Pathophysiological hallmarks of Alzheimer's disease (AD) include extracellular amyloid plaques and intracellular neurofibrillary tangles. Recent studies also demonstrated a role of neuroinflammation in the progression of the disease. Clinical trials and animal studies using low-dose radiation therapy (LDRT) have shown therapeutic potential for AD. This systematic review summarizes the current evidence on the use of LDRT for the treatment of AD, outlines potential mechanisms of action, and discusses current challenges in the planning of future trials.

Methods and Materials: A systematic review of human and animal studies as well as registered clinical trials describing outcomes for RT in the treatment of AD was conducted. We followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Articles published until July 1, 2023, were included.

Results: The initial search yielded 993 articles. After the removal of duplicates and ineligible publications, a total of 16 (12 animal, 4 human) studies were included. Various dose regimens were utilized in both animal and human trials. The results revealed that LDRT reduced the number of amyloid plaques and neurofibrillary tangles, and it has a role in the regulation of genes and protein expression involved in the pathological progression of AD. LDRT has demonstrated reduced astro- and microgliosis, anti-inflammatory and neuroprotective effects, and an alleviation of symptoms of cognitive deficits in animal models. Most studies in humans suggested improvements in cognition and behavior. None of the trials or studies described significant (>grade 2) toxicity.

Conclusions: Preclinical studies, animal studies, and early clinical trials in humans have shown a promising role for LDRT in the treatment of AD pathologies, although the underlying mechanisms are yet to be fully explored. Phase I/II/III trials are needed to assess the long-term safety, efficacy, and optimal treatment parameters of LDRT in AD treatment. © 2023 Published by Elsevier Inc.

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Introduction

Neuropathological and pathophysiological hallmarks of Alzheimer's disease (AD) include extracellular amyloid ("senile") plaques as well as intracellular neurofibrillary tangles (NFTs).[1,2] In addition, neuroinflammation is considered the third major hallmark of AD pathology.[3] Current therapeutic treatment options are focused on alleviating the clinical symptoms of the disease rather than targeting the underlying neuropathological and pathophysiological mechanisms. Despite extensive research efforts, there are only a few treatment options available, which merely decelerate the progress of dementia. Moreover, the failure rate of drugs in the drug development pipeline is considerable.[2,4] Recently published preliminary preclinical and clinical evidence suggests that low-dose radiation therapy (LDRT), including low-dose ionizing radiation, might have a potential therapeutic role in treating AD.[5,6] A first narrative review by Wilson et al[7] also highlighted the emerging role of radiation therapy (RT) in AD. In this first systematic review on the topic, we comprehensively assess and update the preclinical evidence and early clinical trials that have explored the use of RT as a treatment option for patients with AD. Furthermore, we discuss potential mechanisms of action, summarize the available data, and derive the most pressing challenges in the execution of future RT trials for AD.

Methods and Materials

A systematic review of the literature was performed in accordance with the guidelines of the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplementary File 1) Supplementary Materials).[8] Variably combined search items included "radiotherapy," "radiation," "dose fractionation," "Alzheimer's disease," and "amyloid." Retrospective and prospective studies in all species were included. PubMed, the Cochrane Library, Embase, and Ovid Medline were used for the literature search. For ongoing clinical trials, ClinicalTrials.gov was used with the following search items: "radiotherapy," "radiation," and "Alzheimer's disease." Databases were searched on July 1, 2023. Only articles published in English were considered. All studies published before July 1, 2023, were included (Table 1). The first reviewer (D Kaul) excluded duplicate entries, studies that included interventions other than RT, and studies that did not match the search items.

Data items

The data items extracted from all eligible studies were author list, publication year, primary objective, subjects (both animals and humans), disease status, dose per fraction, number of fractions, time from RT to sacrifice or analysis, and reported outcomes. All included articles provided information on the aforementioned items, ensuring good validity and comparability across studies. After initial screening of data items by the first reviewer (D Kaul), the second and third reviewer (F Ehret and S Roohani) checked for suitability and accuracy.

Quality assessment

To ensure adequate quality standards for included articles, both the titles, abstracts, and full texts were thoroughly examined by the first reviewer (D Kaul). All resources obtained online were saved as portable document format files in case the online record was edited or removed. Risk of bias was assessed individually for every study by using the Systematic Review Centre for Laboratory Animal Experimentation Risk of Bias tool for animal studies and the

Table 1 Inclusion and exclusion criteria

Category	Inclusion	Exclusion
Study design	Any except those defined in the exclusion section	Narrative reviews Systematic reviews Commentaries on primary research articles and trials
Population	Animals and humans Sex: Any Disease: AD Stage: Any	None
Intervention	LDRT WBRT RT along with standard drug therapy for AD	All except those defined in the inclusions section
Outcome	Aβ plaques or NFTs Cognitive, physical, and/or behavioral abilities	N/A
Date range	Until July 1, 2023	

Abbreviations: Aβ = amyloid-beta; AD = Alzheimer's disease; LDRT = low-dose RT; N/A = not applicable; NFT = neurofibrillary tangles; RT = radiation therapy; WBRT = whole brain RT.

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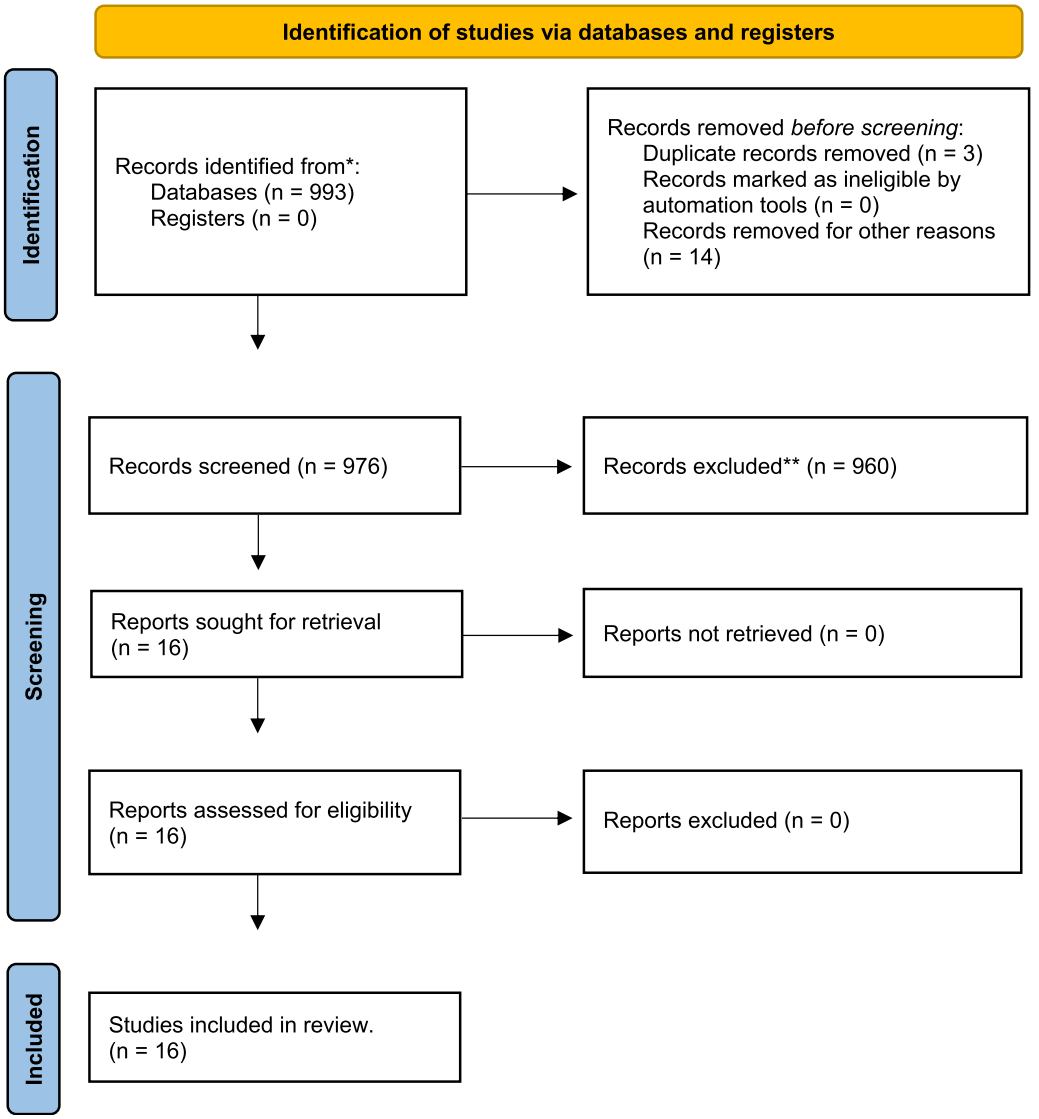

Fig. 1. Flow diagram for study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Newcastle-Ottawa Scale for human studies (Supplementary Materials).[9,10] After the initial evaluation by the first reviewer (D Kaul), the second and third reviewer (F Ehret and S Roohani) critically edited the bias assessment and the list of results. They also added further articles if deemed necessary.

Results

The PRISMA flow diagram (Fig. 1) shows all initial search results, excluded articles, screened articles, and the final number of articles included, based on the prespecified inclusion and exclusion criteria. Systemically reviewed studies on RT in AD are summarized in Tables 2 (animals) and 3 (humans), while ongoing clinical trials are summarized in Table 4.

Effects of RT in the treatment of AD in animal models

Marples et al[6] provided the first evidence of RT reducing amyloid-beta (Aβ) plaques. Thirty-week-old Aβ-overexpressing amyloid precursor protein (APP)/PS1 mice were irradiated and investigated. The authors tested single doses (5 Gy, 10 Gy, and 15 Gy) and fractionated doses (10 × 1 Gy, 5 × 2 Gy, and 10 × 2 Gy) to the hemibrain. They found the most significant reductions in the number and size of Aβ plaques at 8 weeks (compared to 2 and 4 weeks) after single dose and fractionated regimens. Fractionated RT produced a more effective reduction in plaques than single doses of comparable biologically effective dose. This finding was interpreted as a sign that the effects were not owing to DNA damage, because in this case effect size would have to

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Table 2 Summary of all systemically reviewed studies on RT for AD in animal models

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and sacrifice or analysis	Outcome		
						Outcome parameters	Results	Conclusion
Ceyzériat[11]	To study the therapeutic potential of 2 schedules of LDRT (weekly and daily)	Advanced amyloid pathology	5 fractions of 2 Gy delivered once daily (cohort 1) 5 fractions of 2 Gy delivered once weekly (cohort 2) Sham irradiation: Only anesthesia without irradiation Target volume: Hemisphere	14-month-old TgAD female rats (n = 10) 15-month- old TgAD female rats (n = 10) Sham irradiation rats (n = 10) WT rats (n = 10)	4 months	Spatial working memory - (alternative Y maze test) Locomotion - OFT Amyloid plaques in hippocampus and cortex Astrocyte reactivity Microglial reactivity	Daily schedule: Significant improvement in memory performances (P = .032) Reduction in total distance travelled as compared with sham-RT (P = .044) Weekly schedule: Significant decrease in locomotion (P = .045) Increased microglial reactivity. Both: No impact on amyloid plaques in the H or C. No impact on astrocyte reactivity.	Daily LDRT improved memory and restored locomotion. Both daily and weekly LDRT did not impact amyloid plaques in the H or C.
Ceyzériat[12]	To evaluate if antiamyloid and anti-inflammatory effects of LDRT can be observed at an early stage of AD	Early stage	5 fractions of 2 Gy delivered once daily Sham irradiation: Only anesthesia Target: Whole brain	12-month-old 3xTg-AD mice (n = 8) Sham-treated 3xTg-AD mice (n = 7) Sham-treated WT mice (n = 8)	8 weeks	Behavior: Open field, elevated plus maze, alternative Y maze amyloid load, tauopathy, neuroinflammation in histology and/or ELISA	No effect on cognitive performance Significant reduction of β42 aggregated forms (−71%) in the H No effect on tauopathy. Trend for neuroinflammation inmarker reduction.	When applied at early stage, LDRT reduces amyloid load and possibly neuroinflammation markers, with no effect on tauopathy

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Table 2 (*Continued*)

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and sacrifice or analysis	Outcome		
						Outcome parameters	Results	Conclusion
Ceyzériat[13]	To evaluate the potential of 5 × 2 Gy daily in 9-month-old TgF344-AD rats, modeling at a presymptomatic stage of AD	Presymptomatic	5 fractions of 2 Gy delivered once daily Target: Hemisphere	TgF344-AD rats (n = 12) Sham-treated TgF344-AD (n = 10) Sham-treated WT (n = 10)	1 month	Behavior: Alternative Y maze, open field, elevated plus maze TSPO-mediated neuroinflammation, secreted CLUSTERIN soluble and aggregated forms of Aβ40, Aβ42, and Aβ oligomers sAPPα	Increase of anxiety after LDRT and sham irradiation. Decrease of the 18-kDa TSPO and secreted CLUSTERIN Decrease of amyloid ($P < .01$; soluble and aggregated forms of Aβ40, Aβ42, and Aβ oligomers) Improved sAPPα levels	LDRT can reduce amyloid deposition and neuroinflammation, when applied before symptoms onset. Higher activation of the nonamyloidogenic pathway
Chicheva[14]	To demonstrate the effect of combined ionizing radiation on the behavior of animals in mouse transgenic models of AD	Cerebral amyloidosis and tauopathy	Combined ionizing radiation: γ rays, 0.24 Gy, 661.7 keV (whole body) After 6 hours ^{12}C, 0.18 Gy, 450 MeV (head region) Control groups: Sham radiation	12-month-old male transgenic 5xFAD mice with cerebral amyloidosis (n = 18) TauP301S mice with τ-pathy (n = 19) Respective age-mate control mice (n = 13)	12 days	MWM Odor recognition test Passive avoidance conditioning Locomotion-OFT	5xFAD group: Better recognition of odors ($P = .09$) TauP301S group: Increased duration of hole sniffing ($P = .02$) Increase in the distance travelled ($P = .01$) Control group: Significant improvement in MWM training ($P = .014$) Increased number of nose pokes ($P = .005$) Increased duration of hole sniffing ($P = .03$)	Significant improvement of spatial learning and stimulation of locomotor and exploratory behavior in WT. Anxiolytic effect and stimulation of locomotor and exploratory behavior in tauopathy mice. Improved learning in odor recognition in mice with cerebral amyloidosis.

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Table 2 (*Continued*)

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and sacrifice or analysis	Outcome		
						Outcome parameters	Results	Conclusion
Hinshaw[15]	To investigate the influence of sex and AD comorbidity on neurobehavioral and pathological changes after whole-body proton exposure in mice.	Disease (AD) present	Whole body, proton irradiation 0, 0.5 Gy or 2 Gy WT: Sham irradiation	4-month- old M and F WT and APPswe/PS1dE9 Tg mice	7-8 months	Cognitive behaviors (spatial memory, fear memory, anxiolytic behavior, stress-induced behavior) Noncognitive behaviors (locomotor activity, strength, endurance, motor coordination and learning) Aβ loads in Tg mice Plasma cytokines	Modest effects of dose, genotype, sex, and their interactions on cognitive and noncognitive outcomes. Modest reduction in the Aβ load in M and effects were long-term. No long-term effect on systemic cytokine levels	Trend towards reduction of Aβ and microglial activation in M Tg after 2 Gy. No long-term impact of proton irradiation on microhemorrhages, hippocampal synaptic, and dendritic density, or most of the assayed plasma cytokines
Iacono[16]	To determine whether a single exposure to LDRT on a large mammalian brain could produce molecular-level changes that could potentially generate a scientific rationale for the future applications of LDRT as a preventive or therapeutic tool for different neurodegenerative disorders in humans.	Healthy	Single, 1.79 Gy dose Target volume: Whole body	M Gottingen minipigs ranging in age from ~ 6.0 to 6.5 months. Sham + vehicle (n = 4) Radiation+ vehicle (n = 6) Sham + captopril (n = 6) Radiation + captopril (n = 6)	4 weeks	Protein expression: Ptau, APP, GAP43, GFAP, and DNA-polymerase-β levels.	Radiated animals had lower levels of pTau in FC (P = .018) and H (P = .038), APP proteins in CRB (P = .0039) and H (P = .0009), GAP43 expression in CRB (P = .51) as compared with sham animals. Radiated animals had higher GFAP levels in H (P = .007), DNA-polymerase levels in FC (0.0019) as compared with sham animals. No changes in IBA-1 and MBP expressions in radiated vs sham animals.	The results suggest that LDRT might act as a potential tool that can interfere with the accumulation of specific proteins linked to the pathogenesis of various neurodegenerative disorders.

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Table 2 (*Continued*)

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and sacrifice or analysis	Outcome		
						Outcome parameters	Results	Conclusion
Khan[17]	To investigate the neuroprotective role of fractionated X-irradiation in Aβ1−42-based rodent model of AD	Aβ1−42-induced neurotoxicity (4 weeks)	10 Gy X-irradiation (fractionated dose, 2 Gy × 5 days) after 4 weeks of Aβ1−42 peptide infusion	SD F rats sham control (group 1), Aβ1−42 injected (group 2), cranial X-irradiated (group 3) and Aβ1−42 injected followed by cranial X-irradiation (group 4).	4 weeks	Motor function tests: Locomotor activity and muscular strength Cognitive tests: Active avoidance test, passive avoidance test, MWM, elevated plus maze test Neurochemical and neurotransmitters	Significant decrease in amyloid deposits was observed in the Aβ1−42 + irradiated animals. Significant improvement in Aβ1−42-induced memory impairment in the animals subjected to fractionated cranial X-irradiation.	Fractionated X-irradiation has the ability to curtail the Aβ1−42-based neurotoxicity in AD or other similar pathologies.
Kim[18]	To reconfirm that LDIR reduces Aβ deposition and improves cognitive deficits. To elucidate the mechanisms of LDIR-induced inhibition of Aβ accumulation and memory loss in AD.	Disease (AD) present	Total radiation dose of 10 Gy in 5 fractions	6-month-old M heterozygous 5XFAD transgenic mice WT littermates of 5XFAD mice were used as controls.	8 weeks	Reduction in Aβ deposits Spatial learning and memory (MWM) Examination of M1 and M2 cytokines	LDIR inhibits Aβ deposition and improves cognitive deficits in 5XFAD mice. LDIR regulates Aβ-induced production of inflammatory cytokines in the 5XFAD mice. LDIR directly induced phenotype switching from M1 to M2 in the brain with AD.	LDIR modulates LPS- and Aβ induced neuroinflammation by promoting the production of M2-associated cytokines and therefore has the potential to alleviate Aβ-deposition and memory loss.

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Table 2 (*Continued*)

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and sacrifice or analysis	Outcome		
						Outcome parameters	Results	Conclusion
Kim[19,20]	To examine the effect of LDIR on Aβ accumulation and Aβ -mediated pathology.	Disease (AD) present	Total of 9 Gy, 1.8 Gy per fraction for 5 consecutive days	4-month-old F 5XFAD mice 21 mice divided into groups of 7. 1) WT mice, (2) sham-exposed 5XFAD mice, and (3) LMDIR-exposed 5XFAD mice	4 days	Effect on Aβ accumulation Effect on synaptic and neuronal loss Effect on neuroinflammation and cytokine production	LDIR did not affect Aβ accumulation in the brain, but significantly ameliorated synaptic degeneration, neuronal loss, and neuroinflammation in the H formation and cerebral cortex	LDIR has neuroprotective and anti-inflammatory effects against Aβ accumulation and Aβ -mediated pathology in neurodegenerative diseases like AD.
Marples[6]	To investigate if cranial X-irradiation reduces Aβ plaques and influences cognitive function in a transgenic mouse model of AD.	Early onset AD	Cohort 1. Single dose of 5, 10, or 15 Gy Cohort 2. Fractionated doses of 1 Gy × 10, 2 Gy × 5, or 2 Gy × 10 Target volume: Hemisphere	M B6. Cg-Tg AD-prone mice	At 24 h, 2, 4, 8 weeks	Effect on Aβ plaques Spatial learning and memory (MWM)	Single continuous treatment of RT irrespective of dose and sacrifice time significantly reduced Aβ plaque burden ($P = .00048$) Fractionated LDRT also significantly reduced Aβ plaque burden ($P < .003$) The reduction in Aβ plaque burden is associated with cognitive improvements ($P = .012$)	Brain irradiation using single dose as well as fractionated doses reduces the Aβ plaque burden and reduces cognitive deficits.
Wilson[21]	To investigate the effects of radiation in an age-matched series of 3xTg-AD mice.	Disease (AD) present	5 fractions of 2 Gy to right hemisphere, for 5 consecutive days	Six F (3xTg-AD) mice Age 16 months	8 weeks	Effect on Aβ plaque burden Effect on NFT	Significant reduction in Aβ plaque burden ($P = .028$) and reduction in neurofibrillary tangles ($P = .0024$)	LDRT reduces Aβ plaque burden and it also reduces tau-associated NFTs.

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Table 2 (*Continued*)

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and sacrifice or analysis	Outcome		
						Outcome parameters	Results	Conclusion
Yang[22]	To determine the appropriate RT dose and schedule for AD treatment. To investigate therapeutic effects and mechanisms of low RT for AD.	Late-stage AD	LD-LDRT group: 3 Gy (5 × 0.6 Gy) LMD-CDRT group: 10 Gy (5 × 2 Gy) Sham group: without RT Target volume: Whole brain	8-9-month-old FxFAD mice Nontransgenic littermates were used as controls.	Every week after RT for 4 weeks	Effect on proinflammatory cytokines (CD54, IL-3, CXCL9/10, and CCL2/4)	Reduced level of proinflammatory cytokines (CD54, IL-3, CXCL9/10, and CCL2/4) in the hippocampus of 5xFAD mice as compared with WT sham mice. Reduced microgliosis and decreased amyloid plaque burden in the H. Attenuated cognitive impairment.	LD-LDRT (3 Gy in 5 fractions) improves cognitive impairment and reduces the deposition of Aβ plaque by regulating neuroinflammation in the late stages of AD.

Abbreviations: 3xTgAD = triple transgenic AD; Aβ = amyloid-β; AD = Alzheimer's disease; APP = amyloid precursor protein; CCL2/4 = chemokine (C-C motif) ligand 2/4; CD54 = cluster of differentiation 54; CRB = cerebellum; CXCL 9/10 = chemokine (C-X-C motif) ligand 9/10; ELISA = enzyme-linked immunosorbent assay; F = female; FC = frontal cortex; FxFAD = 5 AD-linked mutations familiar AD; GAP43 = growth associated protein 43; GFAP = glial fibrillary acidic protein; H = hippocampus; IBA-1 = ionized calcium-binding adaptor molecule 1; IL = interleukin; LDIR = low-dose ionizing radiation; LD-LDRT = low total dose with low dose per fraction; LDRT = low-dose RT; LMD-CDRT = low-moderate total dose with conventional dose per fraction; LMDIR = low−moderate dose ionizing radiation; LPS = lipopolysaccharide; M = male; MBP = myelin basic protein; MWM = Morris water maze; NFT = neurofibrillary tangles; OFT = open field test; RT = radiation therapy; sAPPα = soluble amyloid precursor protein α; SD = Sprague-Dawley; Tg = transgenic; TSPO = translocater protein; WT = wild type.

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Table 3 Summary of all systemically reviewed studies on RT for AD in humans

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and analysis	Outcome		
						Outcome parameters	Results	Conclusion
Cuttler[23]	To describe the improvement in a patient with advanced AD in hospice who received 5 CT scans of the brain.	Advanced AD	5 CT scans, each with a dose of 40 mGy, over a period of 3 months	81-year-old human woman	Patient was examined by her neuropsychologist after her 5th CT scan.	Any sign of change in her cognitive abilities, motor function, verbal responses, or memory etc.	Sign of old memory return (patient remembered her daughter's old roommate's name) Improvement in motor function (patient lifted her leg and made several head turns) Improvement in verbal responses (Patient started responding in 3-5 word sentences or shorter responses like "yes" or "no")	Patient showed remarkable cognitive and physical improvement during the first 4 scans. However, the fifth scan resulted in a significant setback. Soon after the patient continued to improve, she was released from hospice care.
Cuttler[24]	To determine whether the previously reported benefits of LDIR in a single case with AD could be observed again in other cases with AD when the same treatments are given.	Clinically stable, advanced stage dementia	3 Consecutive treatments each spaced 2 weeks apart (0.04-0.089 Gy)	4 Human participants 3 men aged 88, 90, and 84 years and 1 woman aged 82 years	6 weeks	Qualitative data on patient's ability to communicate and interact. Quantitative measures: Neurocognitive abilities (SIB) Behavioural symptoms (CMAI) Functional abilities (ADFACS)	Case 1 (88/M): No changes on ADFACS score Slight changes in CMAI scores. Initial improvement in SIB score. Case 2 (90/M): No changes in the quantitative scores or qualitative observations. Case 3 (84/M): No significant improvements in the ADFACS, SIB, or CMAI scores. Patient showed occasional alertness and cooperation. Case 4 (82/F): Patient showed no quantitative improvements after first 2 treatments. Slightly improved ADFACS and SIB scores just before her third treatment. She became more alert, pleasant, and cooperative during the treatments.	Qualitative data showed improvement in cognition and behavior. There were few meaningful improvements on the 3 quantitative outcome measures ADFACS, CMAI, SIB

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Table 3 (*Continued*)

First author	Primary aim	Disease status	Radiation regimen	Subjects	Time between RT and analysis	Outcome		
						Outcome parameters	Results	Conclusion
Kim[25]	To determine whether LDRT is effective in patients with AD.	Mild-to-moderate AD	5 fractions of 0.5 Gy 3 times a week	5 humans with a mean age of 71.8 years (range 60-83); 5 women	6 months (interim analysis)	Seoul Neuropsychological Screening Battery at 3 and 6 months 18F-florapronol PET at 3 months	Neurological improvement was seen in 1 patient. One patient showed a temporary improvement in CDR-SB, 2 patients showed stable improvement in the K-MMSE score 2 Two patients complained of mild nausea and mild hair loss during treatment	LDRT is tolerable in patients with AD. 12 months follow-up is awaited
Rogers[26]	To report neurocognitive, imaging, ophthalmologic, and safety outcomes after LD-WBRT for patients with early Alzheimer dementia treated on a pilot trial.	Early AD	5 fractions of 2 Gy over 5 days Target volume: Whole brain	5 humans with a mean age of 73.2 years (range 69-77); 2 males, 3 women	At 6 week, 3, 9, 12 months	NCF PF QOL	MMSE-2 T scores: 3 patients improved, 1 remained stable, and 1 declined. Stable naming skills over time HVLT-R learning and memory skills declined over time for 3 patients, 1 showed improvement, and 1 showed no change from the baseline. BVMT-R learning and memory skills mildly declined in 3 patients and improved in 2 patients. Declining trend in psychomotor processing speed while mental processing speed, attention, visuospatial skills were generally stable. Mood and QOL remained stable	Positive safety profile for the treatment Treatment stabilizes/improves cognitive functions. Only side effect reported was temporary epilation with satisfactory hair growth

Abbreviations: AD = Alzheimer's disease; ADFACS = Alzheimer's Disease Functional Assessment and Change Scale; BVMT-R = Brief Visuospatial Memory Test − Revised; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CMAI = Cohen-Mansfield Agitation Index; CT = computed tomography; HVLT-R = Hopkins Verbal Learning Test − Revised; K-MMSE = Korean Mini-Mental State Examination 2nd edition; LDIR = low-dose ionizing radiation; LDRT = low-dose RT; LD-WBRT = low-dose whole-brain RT; MMSE-2 = Mini-Mental State Examination - Second Edition; NCF = neurocognitive function; PET = positron emission tomography; PF = psychological function; QOL = quality of life; RT = radiation therapy; SIB = Severe Impairment Battery.

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Table 4 Currently ongoing and recruiting trials on RT for AD

NCT number/ phase	Title	RT dose and fractions	Outcome measures	Dates	Center and location
NCT05635968/ Phase II[27]	The Clinical Trial of Low-Dose Irradiation for Alzheimer's Disease	4 cGy × 6 = 24 cGy vs 50 cGy × 6 = 300 cGy	1. Changes in cognitive function 2. Number of adverse events	Actual study start date: July 15, 2022 Estimated study completion date: April 15, 2024	Kyung Hee University Hospital at Gangdong Seoul, Republic of Korea
NCT04203121/ Phase N/A[28]	The Safety and Scientific Validity of Low-dose Whole Brain Radiotherapy on Brain Amyloidosis During the Treatment of Mild or Moderate Alzheimer's Disease	1.8 Gy × 5 = 9 Gy vs 1.8 Gy × 3 = 5.4 Gy	1. Evaluate low-dose whole-brain RT in subjects with early AD 2. Change in brain amyloid deposits	Actual study start date: April 1, 2019 Estimated study completion date: July 31, 2020	Kyung Hee University Hospital at Gangdong Seoul, Republic of Korea
NCT03352258 / Phase N/A[29]	Effect of Low-Dose Radiotherapy on Brain Amyloidosis in the Treatment of Alzheimer's Disease	2 Gy × 5 = 10 Gy	1. Safety and adverse events associated with low-dose brain RT 2. Change in brain amyloid deposits 3. Neuropsychological performances	Actual study start date: November 17, 2017 Estimated study completion date: December 30, 2021	Geneva University Hospital Geneva, Switzerland
NCT02769000/ Phase N/A[30]	Low Dose RT to Reduce Cerebral Amyloidosis in Early Alzheimer's	2 Gy × 5 = 10 Gy vs 2 Gy × 10 = 20 Gy	1. Evaluate toxicity associated with delivery of low-dose fractionated whole brain irradiation 2. Neurocognitive function 3. Psychological functioning	Study start date: May 2016 Actual study completion date: March 15, 2019	Virginia Commonwealth University Richmond, Virginia, United States
NCT02359864/ Phase N/A[31]	Study of Low Dose Whole Brain Irradiation in the Treatment of Alzheimer's Disease	2 Gy × 5 = 10 Gy vs 2 Gy × 10 = 20 Gy	1. To assess adverse events at 6 weeks, 3 months, 6 months, and 12 months posttreatment	Actual study start date: October 1, 2019 Actual study completion date: February 3, 2021	Beaumont Health Farmington Hills, Michigan, United States Beaumont Health Royal Oak, Michigan, United States

Abbreviations: AD = Alzheimer's disease; N/A = Not available; NCT = National Clinical Trial; RT = radiation therapy.

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be a function of biologically effective dose. An increase in ionized calcium-binding adaptor molecule 1 (IBA-1) positive cells and a trend of increased interleukin (IL)-10 after irradiation were interpreted as a signal of a proinflammatory mechanism induced by RT. Other authors have replied to this interpretation and suggested these findings to be a consequence of an anti-inflammatory response.[32] The authors also investigated cognitive effects of whole brain RT (5 × 2 Gy) in 64-week-old mice 8 weeks after RT. Irradiated mice showed improved performance in the Morris water maze test.[6] In other studies, the authors investigated the effect of prophylactic irradiation on the development of Aβ plaques. Ten-week-old mice received a dose of 5 × 2 Gy to 1 hemisphere. Six months later, the authors found a significant reduction in plaques of 35% in the cortex and 8% reduction in the hippocampus.

These observations were confirmed by Wilson et al[21] in 14-month-old triple transgenic AD (3xTg-AD) mice. The dose regimen was 5 × 2 Gy to the hemisphere of each mouse. The results showed a significant reduction in number and burden of Aβ plaques in the irradiated brain area. Moreover, the authors reported a reduction in tau-associated NFTs 8-weeks post-RT. The authors noted that the decrease in Aβ plaques was more pronounced than that of tau, which they suggested to align with the amyloid cascade model of AD pathogenesis. However, they noted that when discussing the amyloid cascade, it should be kept in mind that in some studies, immunotherapeutics against Aβ or tau had the ability to reduce both of these AD hallmarks, suggesting a synergistic mode of action.[33,34]

Ceyzériat et al[11] then investigated 2 dosing schedules (5 × 2 Gy delivered in 1 week or delivered in 5 weeks) of fractionated LDRT in a TgF344 rat model (Tg-AD) at 15 months to the hemisphere. They discovered that, in contrast to the weekly irradiated group, the group treated daily showed improved memory performances and locomotion after 4 months. Unlike the results obtained from previous studies, a cumulative LDRT dose of 5 × 2 Gy delivered weekly or daily did not affect the amyloid deposits, that is, plaque number and plaque density, in the hippocampus or cortex after 4 months. These findings contradict the results by Marples et al[6] and Wilson et al[21], a potential reason being the advanced stage of AD pathology or the time difference between RT and analysis, that is, 4 months, which was longer than in previous studies. A slight increase in hippocampal astrocyte and microglial reactivity was observed in the weekly irradiated group.[5]

In their second work on AD, Ceyzériat et al[12] used whole brain LDRT of 5 × 2 Gy over 5 days in 12-month-old 3xTg-AD mice. Mice underwent behavioral tests before and 8 weeks after treatment. Amyloid load, tauopathy, and neuroinflammatory markers were evaluated. The authors found a significant decrease of aggregated Aβ42 in the hippocampus. Neuroinflammation showed a tendency to be lowered by LDRT. However, tauopathy and cognitive performances were not improved.

In a third study by Ceyzériat et al, 9-month-old, presymptomatic TgF344-AD rats were irradiated and received 5 × 2 Gy to 1 hemisphere. One-month after irradiation, neuroinflammation markers and amyloid plaque accumulation were assessed. Eighteen-kDa translocator protein (TSPO) levels, indicative of neuroinflammation and increased in unirradiated animals, decreased after LDRT in the irradiated hemisphere and the nonirradiated hemisphere. Levels of the secreted inflammatory protein clusterin (sCLU) were elevated in unirradiated TgAD rats, with LDRT decreasing sCLU levels to normal levels in both hemispheres of the brain. Both soluble (Tx-soluble) and aggregated (Gua-soluble) forms of Aβ40 and Aβ42 were reduced by LDRT in the hippocampi of the treated and the contralateral hemispheres, and the same effect was observed for Aβ42 oligomers. In addition, LDRT increased levels of soluble APPα, which is associated with the nonamyloidogenic pathway, but it did not alter the amyloidogenic pathway. The authors pointed out that irradiation to one hemisphere also caused effects in the untreated hemisphere. They suggested that soluble factors might be responsible for this effect, which is a hypothesis-generating finding that could potentially open up the possibility to use partial brain irradiation in future trials once this observation has been further investigated.[13]

Iacono et al[16] used a higher order animal model (minipig) to study the effect of a single total-body radiation exposure (1.79 Gy) after 4 weeks. Irradiated animals had lower levels of pTau in the frontal cortex and hippocampus, APP in the hippocampus and cerebellum, growth associated protein 43 in the cerebellum, and higher levels of glial fibrillary acidic protein in the hippocampus versus sham-animals. These findings provided insight into the ability of LDRT to upregulate and downregulate protein expression that can interfere with the pathological development or progression of AD. Because the degree and rate of expression of different proteins varied considerably across the different regions of the brain, the authors suggested that modern RT techniques that can spare certain areas of the brain could lead to a more precise and effective treatment for AD.

A group from South Korea then published 2 studies in 2020. In the first work, Kim et al[19] studied LDRT (5 × 1.8 Gy) in 4-month-old female 5xFAD mice 4 days post-RT. The authors reported no significant changes in the Aβ accumulation in irradiated mice as compared with the control group. However, they found a significant reduction in synaptic and neuronal loss in the hippocampal formation and cerebral cortex as well as reduced microgliosis and astrogliosis in the irradiated mice. Furthermore, a dose of 1 × 1 Gy was found to suppress $A\beta_{1\text{-}42}$-induced neuronal death in the neuroblastoma SH-SY5Y cell line and to inhibit the production of proinflammatory molecules and activation of the nuclear factor-κB pathway in mouse microglia BV-2 cells.

A second study by Kim et al[18] using 6-month-old 5xFAD mice treated with 5 × 2 Gy found that the number of

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microglia and astrocytes were significantly reduced in irradiated mice as compared with unirradiated animals. Furthermore, LDRT also significantly inhibited the production of proinflammatory cytokines. In addition, LDR-modulated lipopolysaccharide induced neuroinflammation by promoting the production of M2-associated cytokines. The authors discussed several mechanisms: M2 microglia are moderately activated cells with associated increased phagocytosis that might help clearing up Aβ proteins, with upregulation of synaptophysin and cell adhesion molecule-enabling synaptic plasticity and promoting synaptogenesis. Moreover, the upregulation of heat shock protein 70 could reduce the neurotoxicity of Aβ. Finally, LDRT could also stimulate the production of vascular endothelial growth factors, which would enable an improved drainage of Aβ.

In a study from India, Khan et al[17] used an AD model using intracerebroventricular and hippocampal Aβ_{1-42} injections. A dose regimen of 5 × 2 Gy was applied. The authors found a significant decrease in amyloid deposits, and neurobehavioral tests showed a significant improvement in memory impairment. The authors also identified downregulation of acetylcholinesterase activity in irradiated animals.

While the majority of the mentioned models studied normofractionated doses, another group from South Korea compared the effects of hyperfractionated LDRT (5 × 0.6 Gy) with normofractionated LDRT (5 × 2 Gy) in 5xFAD mice for the first time.[22] The effectiveness of hyperfractionated LDRT has previously been studied in benign inflammatory-degenerative disorders and has shown widespread efficacy. The authors reported that LDRT can attenuate inflammation in AD, specifically in its later stages. A significant reduction in proinflammatory cytokines was detected and a significant decrease in IBA-1 was found in the hippocampus. These observations were shown in both dose regimens. The authors suggested that RT, particularly LDRT, seems to shift the balance between strongly activated and moderately activated microglia in the hippocampus. RT may break a vicious cycle between neuroinflammation and the accumulation of amyloid plaques.

A recent study by Hinshaw et al[15] was inspired by radiation exposure on interplanetary flies. This was also the first study to investigate both male and female transgenic mice (APPswe/PS1dE9 Tg). The authors performed whole body proton radiation at a dose of 0.5 Gy or 2 Gy of 1GeV protons. They reported modest effects of dose, phenotype, and biological sex characteristics on both cognitive and noncognitive outcomes. They reported modest but long-term effects of RT in the reduction of Aβ load in males but not in females even though female mice showed more Aβ load at baseline. Finally, they showed a modest reduction in the microglial activation in male mice treated with 2 Gy as compared with the sham group.

A work by Chicheva et al[14] was also inspired by interplanetary flies. The authors examined the impact of combined ionizing radiation on cognitive function in male transgenic 5xFAD, TauP301S wild-type mice. They used combined radiation using γ rays (0.24 Gy) to the whole body and ^{12}C (0.18 Gy) to the head. In wild-type mice, an improvement of spatial learning and stimulation of locomotor and exploratory behavior was found. In addition, an anxiolytic effect and stimulation of such behavior were revealed in irradiated mice with tauopathy. Mice with cerebral amyloidosis exhibited improved learning in the odor recognition test.

Effects of RT in the treatment of AD in humans

Publications on humans start with a first case report by Cutler et al[23] on an 81-year-old female with AD who received very low radiation doses using 5 standard computed tomography (CT) scans. The patient showed remarkable improvement in cognition, speech, movement, and appetite during the first 4 scans. However, her condition deteriorated after the fifth CT scan. Each scan delivered approximately 40 mGy.

This case report formed the basis for a pilot study on 4 human participants with clinically stable yet advanced stage dementia. The dosing schedule was similar to that of the case study. The findings suggested remarkable qualitative improvements in cognition and behavior in 3 out of 4 patients. However, the fourth patient did not show any improvement. There were only a few meaningful changes in the quantitative outcome measures.[24]

Rogers et al[26] conducted a pilot trial to investigate the use of RT for the management of early AD in human subjects. Originally, the researchers intended to treat a cohort of 15 patients with 5 × 2 Gy and upon safe completion of the first cohort, another 15 patients were to be treated with 10 × 2 Gy. Because of the coronavirus disease pandemic, the trial ended early after the inclusion of 6 patients with AD (1 screening failure). After LDRT of 5 × 2 Gy, improved Mini-Mental State Examination (MMSE-2) T-scores in 3 patients at 1 year were found, while the scores remained stable in 1 and declined in 1 patient. Similarly, naming, learning, and memory skills remained broadly stable yet within clinically impaired range for 4 out of 5 patients.

In a very recent 6-month interim analysis of a Korean pilot study, Kim et al[25] published data on 5 patients with mild-to-moderate AD treated with 6 × 0.5 Gy (3 times a week). One patient showed a temporary improvement in the Seoul Neuropsychological Screening Battery II. Two patients showed stable improvement in the Korean MMSE-2 score. Two patients complained of mild nausea and mild hair loss during LDRT, which improved after treatment. The authors will conduct cognitive function tests 12 months after LDRT.

Discussion

The role of RT as a possible treatment modality for AD has shown promising early results, but the field is still in its

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nascent stage, and significant research efforts are required to fully comprehend and assess its potential. The positive outcomes seen in mouse models after LDRT are promising, but caution is needed as we interpret these early findings and proceed with further investigations.

Proposed mechanisms of action

A number of studies have suggested cognitive improvements through LDRT in animal models and in humans; however, the mechanisms remain unclear. Several studies suggest a reduction of neuroinflammation through LDRT (Fig. 2).[5,6,13,19,18,22] Le Reun et al[35] suggested that LDRT causes anti-inflammatory effects through interaction with the ATM kinase, which in turn interacts with or phosphorylates certain cytokines. However, the exact mechanisms remain unclear.

Marples et al. observed a trend for increased IL-10 after irradiation. Yang et al found that LDRT seems to shift the balance between proinflammatory and anti-inflammatory microglia in the hippocampus and suggested that RT could break a vicious cycle between neuroinflammation and the accumulation of amyloid plaques. A study by Kim et al.[36] discussed mechanisms in which a population of moderately activated microglia was associated with an increase in phagocytosis, which might help in clearing abnormal Aβ proteins. Ceyzériat et al.[13] found that LDRT leads to a decrease in 18-kDa TSPO levels and decreased levels of sCLU.

Several trials also showed a reduction in amyloid[6,12,13,16,17,36, 21, 37] and tau.[21,16] For instance, Wilson et al. found a significant reduction in the number and burden of Aβ plaques and tau- associated NFTs post-RT. Ceyzériat et al.[13] found LDRT to increase levels of soluble APPα, which is associated with the nonamyloidogenic pathway. Iacono et al.[16] found that LDRT can upregulate and downregulate proteins associated with the pathological development of AD in different areas of the brain. The authors suggested that RT techniques, which can spare certain areas of the brain, might have potential benefits, as the expressional changes of proteins varied across brain regions in their study. Khan et al.[17] identified downregulation of acetylcholinesterase activity in irradiated animals. Ceyzériat et al.[13] highlighted that irradiation to 1 hemisphere caused effects in the untreated hemisphere as well, suggesting that soluble factors might be responsible for this bilateral effect.

Open questions on AD pathophysiology

Soluble and plaque-bound Aβ as well as neurofibrillary MAPtau have an impact on all central nervous system (CNS)-resident cell populations. Neuroinflammation as a

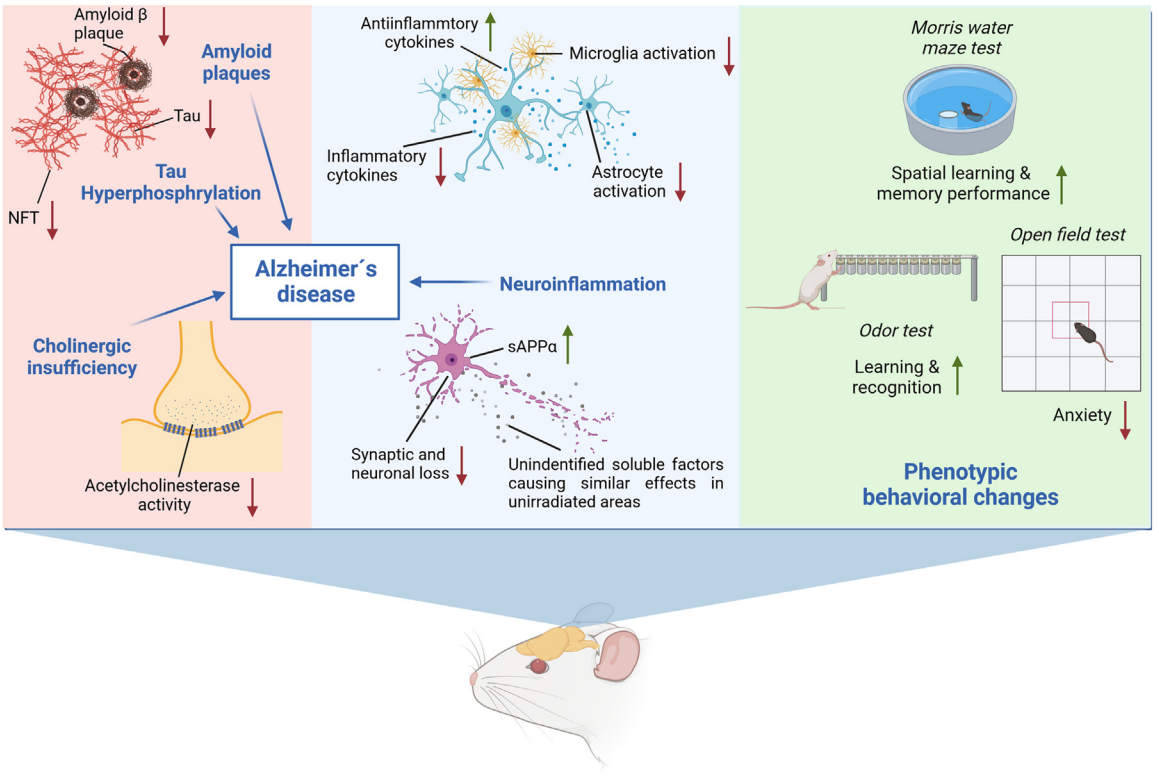

Fig. 2. Overview of effects of low-dose radiation therapy in Alzheimer's disease models. Blue arrows indicate the pathophysiological hallmarks of Alzheimer's disease while red and green arrows indicate effects of radiation therapy. *Abbreviations:* AChE = acetylcholine esterase; sAPPα = soluble amyloid precursor protein α.

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prominent hallmark in AD is a prime example: microglia are the main producers of proinflammatory cytokines in the CNS, but astrocytes also contribute.[38] Neuroinflammation correlates with an increase of Aβ levels in AD mouse models as well as in mild cognitive impairment (MCI), the proposed precursor of AD, in human patients.[39,40] Also, enhanced MAPtau in patients correlates with increased neuroinflammation.[39] Furthermore, RT of brain tumors can lead − depending on dose, brain region, and radiation regime − to inflammatory responses.[41,42] Another intensively researched aspect is the degradation and loss of myelination in AD, mediated by changes in the oligodendrocyte, oligodendrocyte progenitor cells, and also microglia populations,[43−46] which impact neuronal cell populations and cognition.[47,48] Also, demyelination could be induced by RT. Therefore, it is crucial to monitor not only the Aβ and MAPtau load but also the changes in the CNS cell landscape in both clinical trials and preliminary animal experiments.[49,50] This helps gauge disease progression and detect potential harmful effects of irradiation at the earliest opportunity.

For this purpose, omics approaches should be included in future studies. In AD, the assessment of microglia has come far from the dichotomy division into harmful M1 and beneficial M2 microglia. Single nuclei RNA sequencing revealed the existence of different microglia subclusters and states, which are characterized by different transcriptomic signatures, depending on age and brain region, and can change and develop in the various disease settings.[51] A similar change of view has also occurred with regard to astrocytes, where A1 and A2 are not sufficient anymore to describe the different astrocyte states.[52] In AD mouse models, microglia clustered around Aβ plaques develop a unique signature (disease-associated microglia), which differs strongly from microglia away from the plaque.[53,54] Also, in postmortem tissue of human patients with AD, microglia are surrounding the plaques and express some transcript changes similar to disease-associated microglia.[55] In addition, astrocytes, as well as the different neurons, oligodendrocytes, and oligodendrocyte progenitor cells, show distinct alterations in their mRNA profile and number, thus strengthening the rationale for assessing RNA transcripts in RT.[43,56]

While single nuclei RNA sequencing was established as the new standard platform for high-throughput and large-scale screening in the field within the last years, the protein level was often neglected. However, many processes are highly regulated on a protein level, as, for example, IL-1ß production or autophagy.[57−59] Also, transcriptomic alterations do not necessarily reflect changes on the protein level. It would thus be beneficial to supplement the transcriptomic analysis with a proteomics approach using high-throughput mass spectrometry.[60] In addition, proteomics allows not only the quantification but also reveals the composition of Aβ plaques and neurofilaments.[48,61,62] One important question is the choice of the right sample: while brain tissue gives the best insights into the transcriptional and translational changes during or after RT, it requires a brain biopsy. Thus as proxy, cerebrospinal fluid or plasma could be analyzed, which was already used successfully for proteomic and transcriptomic screens in patients with AD or multiple sclerosis.[48,63−67] Considering imaging in humans, it should be mentioned that noninvasive monitoring with positron emission tomography (PET) can be employed to determine Aβ load[68] and neuroinflammation using TSPO tracer.[69,70]

Challenges in trial design and dose finding

The presented preclinical and clinical data suggest a potential role of RT in the management of AD. However, designing a larger phase II/III clinical trial is challenging, given the lack of understanding of underlying pathophysiological processes and their interaction with RT. We identified the following challenges in designing a clinical trial.

Primary endpoint and sample size calculation

Clinically important differences in AD trials are of the utmost importance.[71] However, challenges in determining these differences regarding the endpoint selection remain. This is also relevant for potential RT trials. It is unclear whether these trials should primarily address a neurocognitive endpoint measured by testing (MMSE-2, MoCa, ADAS-Cog13, etc) or surrogate markers, for example, functional PET imaging changes or cerebrospinal fluid biomarkers. However, imaging markers still have a considerable uncertainty and are rarely validated in addition to the unclear clinically meaningful effect. These limitations also apply to cerebrospinal fluid biomarkers such as Aβ1−42, Aβ1−40, phosphorylated tau 181, and total tau.[72] These uncertainties also hamper the calculation of a meaningful trial's sample size, with little to no data on the effect size of RT.

Dose, fractionation, and target volume

As outlined in this review, the data on RT dose and fractionation vary significantly in the preclinical as well as in the clinical studies from CT-based fractionated RT in the mGy range in humans, over hyperfractionated approaches, up to single doses of 15 Gy in murine models. The effectiveness of doses of RT in animals and humans may depend on age, sex, stage of the disease, individual radiosensitivity, time from RT to measurements, and multiple other factors. It should also be noted that doses used in animal models cannot be directly extrapolated to human equivalent doses (human cells are more radiosensitive than murine cells).[73,74] Also, it has been suggested that cells from patients with AD are more radiosensitive.[75] Thirdly, it is a well described radiobiological phenomenon that lower doses of RT can in some cases cause higher biological effects than high doses. One potential explanation for this phenomenon is radio-induced nucleoshuttling of the ATM protein.[35] These radiobiological facts limit the comparability and are of particular importance as the potential effect of RT may only be

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apparent within a specific spectrum of dose and number of fractions and within a certain time period. Choosing a RT regimen is an unsolved challenge for the design of an interventional RT trial. It also remains unclear whether advanced radiation techniques that can spare radiosensitive parts of the brain should be discussed and which areas should be spared. Further preclinical and clinical data are required to determine a range of efficacious and safe doses (eg., National Clinical Trials 04203121 and 05635968).

Toxicity and safety

So far, none of the studies conducted in animal models associated LDRT with any significant short-term or long-term toxicities. The studies in transgenic mouse models of AD provide promising preliminary data, but comprehensive, long-term studies in animals first and later in humans are required to fully assess the safety of this treatment approach. No studies in humans in this review have mentioned any high-grade acute or chronic toxicity post-LDRT, with 1 exception. However, a potential increased long-term radiosensitivity in patients with AD could limit the beneficial effects of RT, especially if reirradiations should be necessary to obtain durable treatment effects. Several clinical trials with toxicity and safety endpoints are ongoing (Table 4).

Patient selection and timing

AD and its precursor, MCI, represent a broad continuum of a neurodegenerative disorder.[72] The slow development of AD implies a year-long process with a continuous spectrum of disease states. It remains unclear how and when exactly RT can modulate the involved neuropathological processes based on AD severity. The scarcity of clinical data prevents insights regarding the ideal time when to irradiate patients with AD, which also concerns the framework of biomarker-based disease, risk stratification, and ideal patient selection. The potential role of a prophylactic RT in MCI, when neurodegenerative disease is already histopathologically apparent, remains unclear and may be the subject of further research.

RT-drug interactions

Current AD treatment involves cholinesterase inhibitors and memantine. Both drugs are well established, but interactions with RT are poorly understood. This issue extends to newer drugs, including aducanumab and lecanemab. These and other monoclonal antibodies may play a future role in the management of AD. As numerous trials with antibodies are ongoing, it will be another potential challenge to determine their compatibility with RT and assess their combined efficacy and safety.[76,77]

Recruitment and adherence

Enrollment of patients into clinical trials is time-consuming and resource intense. This is particularly relevant to AD trials given the nature of the disease, its diagnosis, and the necessity of further support from relatives, caregivers, and legal representatives.[78,79] Further issues may arise in the context of an RT-focused trial, including logistic challenges for the patient and care givers and hesitancy towards radiation. Furthermore, as AD trials aim to comprehensively assess clinical, imaging, and biomarker changes, maintaining patients on the trial and collecting study data are additional challenges to overcome.

Limitations of our work

There are several limitations to the evidence included in this systematic review. Most of the studies did not comprehensively assess the safety and toxicity profile of RT for treating AD. Moreover, the studies were unable to assess whether RT directly or indirectly eliminates Aβ plaques or prevents the formation and deposition of new plaques. There are a lack of data on the molecular mechanisms underlying the effects of LDRT on AD. Several studies applied LDRT at a disease stage that may have been too advanced to reasonably anticipate a reduction in Aβ plaques and markers of neuroinflammation. Moreover, animal models, RT techniques, and dosages varied substantially. This hinders a proper standardized assessment of treatment efficacy.

Limitations of the early clinical trials in humans include their pilot nature, small sample sizes, inhomogeneous dosing, and different types of radiation. Moreover, Rogers et al[26] reported the inability to interpret the imaging results clearly as another limitation. This is because Aβ burdens often appear rather diffused in human models as compared with animal models. Therefore, future studies might benefit from pre- and posttreatment tau-PET imaging or quantitative scoring methods for amyloid PETs, like centiloid scaling.

To our knowledge, this is the first systematic review of the role of RT in AD. In addition to the previously published narrative, nonsystematic review, we provide a comprehensive overview of the current evidence, including an assessment of biases of available studies and unanswered questions related to the underlying AD mechanisms, and we derive current and future challenges for RT-based trials in the field.[7] We hope that this systematic review serves as a valuable summary to inform future RT research in AD.

Conclusion

Overall, while the prospect of using RT for AD is intriguing, it is imperative to underscore the necessity for more extensive and in-depth research in this field. The aim would not only be to confirm these early findings but also to address the outstanding questions and challenges on AD pathophysiology, ensuring a comprehensive understanding of the risks and benefits associated with this treatment strategy. A potential role of LDRT in other neurodegenerative/neuroinflammatory diseases should be evaluated.

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