Letter

Beams of Hope: Shedding New Light on Alzheimer's Treatment with Low-Dose Radiation Therapy

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Alzheimer's disease (AD), the predominant form of dementia, is a progressive neurodegenerative disorder characterized by an inexorable cognitive decline and memory loss. Accounting for 50%–70% of dementia cases, it represents one of the most formidable challenges in modern medicine. The disease pathogenesis, while not fully deciphered, centers on the β-amyloid cascade, a pathological sequence where misfolded β-amyloid peptides aggregate into neurotoxic oligomers, eventually forming characteristic amyloid plaques and neurofibrillary tangles that disrupt neuronal function and viability. Recent therapeutic advances include the Food and Drug Administration's conditional approval of anti-amyloid monoclonal antibodies (aducanumab, 2021; lecanemab, 2023). However, these breakthrough therapies present significant constraints: their efficacy is confined to early stage AD, they demonstrate only modest clinical benefits, and carry a substantial risk of treatment-emergent adverse effects, particularly amyloid-related imaging abnormalities.

Radiotherapy, combined with surgical intervention and pharmacotherapy, is a pivotal modality in cancer treatment. The recent exploration of low-dose radiation therapy (LD-RT) as a potential therapeutic intervention for AD has attracted significant interest from researchers and clinicians alike[1-4]. Traditionally used in oncology to target and eradicate malignant cells, the scope of LD-RT extends beyond cancer treatment, demonstrating its efficacy in addressing benign lesions; amyloidosis affecting organs, such as the tracheal bronchus and orbit; and chronic inflammatory and degenerative conditions, such as osteoarthritis, suggesting its potential against AD's hallmark amyloid plaques and neuroinflammation.

Preclinical investigations have yielded encouraging results, demonstrating LD-RT's capacity to decrease amyloid protein deposits, mitigate neuroinflammation, and enhance cognitive function across different AD mouse models[5-7]. Marples et al. have highlighted a 78% reduction in cerebral Aβ plaques alongside a significant reduction in inflammation markers MIP-2 and IFNγ in B6.Cg-Tg AD mouse models[5]. Similarly, Yang et al. demonstrated that LD-RT could attenuate the levels of pro-inflammatory cytokines in the hippocampus, signifying potential neuroinflammatory modulation[6]. Kim et al.'s findings further support this by showing a microglial transition towards an anti-inflammatory state, enhancing the microenvironment conducive to combating AD pathology[7].

Clinical explorations, notably by Virginia Commonwealth University in 2023, have provided preliminary evidence of LD-RT's therapeutic potential in humans. A study involving five patients with early stage AD undergoing a low-dose whole-brain radiation protocol (2 Gy ×5 fractions) demonstrated not only safety, but also potential cognitive benefits, as indicated by improvements or stability in MMSE-2 scores, enhanced neuropsychological functioning, psychological well-being, and quality of life. Post-treatment PET imaging suggested a reduction in hippocampal amyloid protein, with mild hair loss as the only reported side effect[8]. These findings, coupled with those of another study from South Korea that observed sustained cognitive improvements and minimal adverse effects in patients with AD following LD-RT[9], reinforce the therapeutic promise and safety profile of this modality.

Given the benign nature of AD and the expectation of long-term survival, we are particularly cautious regarding the neurotoxic effects of whole-brain low-dose radiation therapy. Clinical trials for AD utilize significantly lower radiation doses

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(typically 2 Gy×5 fractions[8] or 0.6 Gy×6 fractions[9]) than those for malignant brain tumors, such as brain metastasis (2 Gy×20 fractions). These reduced doses classify the treatment as low-dose radiation therapy, which is expected to minimize severe neurotoxic reactions. The safety and feasibility of this approach are supported by the findings of two key clinical studies[8,9] that highlighted its promise for effective AD management with minimal risk. Moreover, techniques, such as hippocampal-sparing RT, have been refined to further protect cognitive function in patients undergoing radiation therapy, highlighting the potential for patient-specific treatment optimization.

The integration of preclinical and clinical findings underscores the potential of LD-RT as a novel therapeutic avenue for AD; however, critical questions remain before its widespread clinical adoption. While existing studies highlight LD-RT's ability to reduce amyloid burden and modulate neuroinflammation, deeper mechanistic insights are essential to optimize its application. Future preclinical work should prioritize the elucidation of specific radiation parameters, such as radiotherapy dose, fractionation, and target volume. Animal models can help identify dose thresholds that maximize therapeutic effects while minimizing off-target effects on normal neural tissues and toxicities.

Translating these insights into human trials requires the careful design of clinical studies. Randomized controlled trials with robust cognitive endpoints and longitudinal biomarker monitoring (e.g., amyloid-positron emission tomography) are needed to validate LD-RT's efficacy and establish standardized protocols. It is equally important to investigate LD-RT's synergistic potential with emerging AD therapies, particularly anti-amyloid immunotherapies and anti-tau agents. The interplay between radiation-induced microglial reprogramming and drug-mediated pathology clearance warrants special attention as combination approaches may address AD's multifactorial nature more effectively than monotherapy alone.

Practical considerations, such as refining hippocampal-sparing techniques and developing predictive biomarkers for patient stratification, must accompany these efforts. Long-term safety assessments are crucial, especially given the extended lifespans of patients with AD compared with oncology populations where radiation is traditionally used. By addressing these challenges through interdisciplinary collaboration, the field can advance LD-RT from an experimentally promising to a clinically viable intervention, potentially offering a much-needed tool in the fight against neurodegenerative diseases. In this study, we aimed to establish an interdisciplinary knowledge bridge that familiarizes AD researchers (particularly those in neuroscience and geriatric medicine) with this emerging therapeutic paradigm from radiation oncology.

Competing Interests The authors declare no conflicts of interest.

Ethics Not applicable

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