Neurosurgical Subspecialties **2025** vol. 1(3) | 125–135
DOI: 10.14218/NSSS.2025.00028

Review Article

State-of-the-art Multimodal Imaging and Therapeutic Strategies in Radiation-induced Brain Injury: A Comprehensive Review

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Received: May 30, 2025 | **Revised:** August 09, 2025 | **Accepted:** August 13, 2025 | **Published online:** September 18, 2025

Abstract

Radiotherapy remains one of the essential treatment modalities for brain gliomas, brain metastases, pediatric neuroblastomas, and primary central nervous system lymphomas. With continuous advancements in modern radiotherapy techniques, patients have achieved significantly improved local control rates and prolonged survival. However, the long-term complications associated with radiotherapy have become increasingly evident. Radiation-induced brain injury (RIBI) is a clinical syndrome characterized primarily by neurological dysfunction following focal or whole-brain radiotherapy. It negatively impacts patients' quality of life and imposes a considerable burden on families and society. With the rapid development of medical imaging and artificial intelligence technologies, multimodal imaging techniques, including structural magnetic resonance imaging, diffusion-weighted imaging, functional magnetic resonance imaging, perfusion imaging, positron emission tomography-computed tomography metabolic imaging, and radiomics, have demonstrated significant potential for early detection, dynamic monitoring, and quantitative evaluation of RIBI. Meanwhile, treatment strategies for RIBI are shifting from traditional symptomatic and supportive care toward multidimensional interventions aimed at protecting the blood-brain barrier, modulating neuroinflammation, and implementing precise targeted therapies. Additionally, emerging studies have explored neuromodulation techniques and gut-brain axis regulation, offering new directions for the prevention and treatment of RIBI. Although conventional imaging methods remain valuable for diagnosing RIBI, they exhibit notable limitations in the early stages of the disease and in differentiating RIBI from tumor recurrence. This review focuses on the current state of technological development, key findings, and existing limitations, with the aim of providing a theoretical foundation and technical support for the early identification and precise intervention of RIBI.

Introduction

Radiation-induced brain injury (RIBI) is a significant complication following cranial radiotherapy, characterized by central nervous system dysfunction. While advances in radiotherapy techniques and systemic therapies have substantially improved overall survival in brain tumor patients, these gains have been offset by a rising incidence of RIBI, which adversely affects survivors' quality of life.[1]

Early clinical observations highlighted the harmful effects of nuclear radiation on the developing brain.[2] Subsequent research has confirmed that cranial radiotherapy increases the risk of learning difficulties, mood disturbances, and psychiatric disorders.[3,4] Although preclinical studies suggest that early intervention may mitigate RIBI symptoms, no universally accepted strategy exists for preventing or reversing the condition. Consequently, the early diagnosis, prevention, and management of RIBI have become key areas of current research.

This review provides a comprehensive summary of recent advances in multimodal imaging diagnostics, including structural magnetic resonance imaging (MRI), diffusion/perfusion modalities, magnetic resonance spectroscopy (MRS)/positron emission tomography (PET), and radiomics, as well as evolving therapeutic strategies for RIBI. Our analysis critically examines the current strengths and limitations of these approaches, identifies gaps in the evidence, and proposes future directions to support early de-

Keywords: Radiotherapy; Radiation injuries; Brain injuries; Magnetic resonance imaging; Diffusion magnetic resonance imaging; Radiomics; Artificial intelligence; Neuroinflammation.

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How to cite this article: Wang X, Li S, Yu F, Cui X. State-of-the-art Multimodal Imaging and Therapeutic Strategies in Radiation-induced Brain Injury: A Comprehensive Review. *Neurosurg Subspec* 2025;1(3):125–135. doi: 10.14218/NSSS.2025.00028.

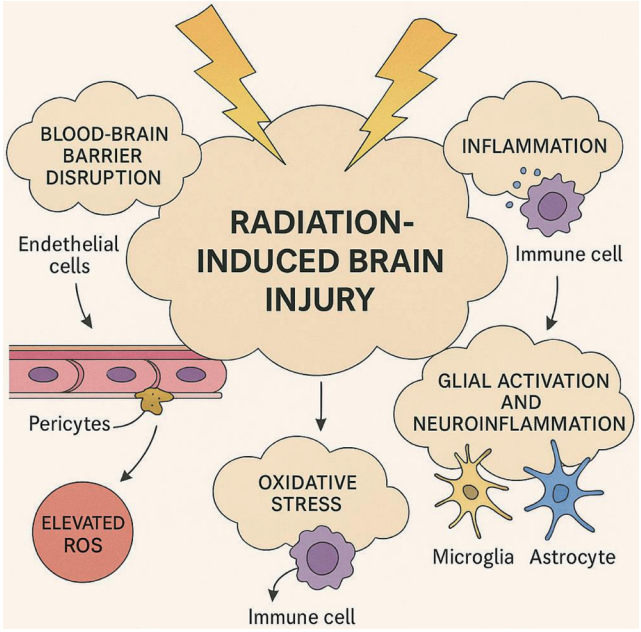

Fig. 1. Mechanisms of radiation-induced brain injury at different post-radiotherapy time points. Radiotherapy induces DNA damage and oxidative stress, leading to endothelial injury and blood-brain barrier disruption, which triggers neuroinflammation, microvascular dysfunction, and neuronal apoptosis, ultimately resulting in progressive edema, demyelination, and irreversible brain necrosis. Created with BioRender.com. ROS, reactive oxygen species.

tection and precision management of RIBI in clinical practice. To conduct this review, we searched PubMed, Embase, and Web of Science for studies published up to July 2025, using combinations of keywords such as radiation-induced brain injury, multimodal imaging, MRI, PET, radiomics, and therapeutic strategies. We included peer-reviewed original studies and reviews addressing RIBI pathophysiology, diagnostic imaging, or interventions, while excluding non-English articles, case reports, and publications lacking substantive data.

Pathophysiological mechanisms of RIBI

RIBI is a multifactorial, delayed-onset neurological disorder.[5] Its pathogenesis involves a confluence of physiological and pathological processes, including neuronal damage, blood-brain barrier (BBB) disruption, inflammatory responses, cerebrovascular alterations, and aberrant activation of glial cells (Fig. 1).[6–9]

Blood-brain barrier disruption and endothelial cell injury

Ionizing radiation directly damages cerebral microvascular endothelial cells, leading to increased BBB permeability. Vascular injury can manifest within 24 h post-radiotherapy. This disruption facilitates the extravasation of plasma proteins and the infiltration of activated leukocytes and inflammatory mediators into the central nervous system, exacerbating local inflammation. Early imaging and pathological studies have established a correlation between vascular pathology and cognitive deficits.[10–12] Autopsy findings in patients with delayed RIBI reveal widespread vascular abnormalities and demyelination of cerebral white matter.[13] Radiation has been shown to activate the phosphatidylinositol 3-kinase – protein kinase B (PI3K-AKT) pathway in astrocytes, reducing autophagy and leading to over-secretion of vascular endothelial growth factor, which contributes to BBB damage.[14]

Radiotherapy also leads to intracranial vascular occlusion, characterized by shortened vessel length and reduced capillary density. Brown *et al*.[15] observed significant reductions in vascular density and length in irradiated rat brains, correlating with cognitive decline over time. Radiation-induced damage to vascular endothelial cells, coupled with reductions in vascular density and length, compromises BBB integrity, representing an early stage of RIBI.

Inflammatory cytokines and biomarkers of RIBI

RIBI is a complex process involving the interplay of various inflammatory and cellular cytokines. Studies have shown that radiotherapy activates N-methyl-D-aspartate receptors, increasing intracellular calcium levels and activating calcineurin. The nuclear factor of activated T-cells (NFAT3/c4), a downstream target of calcineurin, translocates to the nucleus and promotes transcriptional activity, resulting in neuronal apoptosis.[16] Additionally, activation of the kynurenine pathway has been associated with RIBI. Following whole-brain radiotherapy, the kynurenine pathway is significantly activated, characterized by decreased tryptophan levels and increased activity of indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. Elevated levels of kynurenic acid and quinolinic acid can induce oxidative stress, inflammation, nitric oxide pathway dysregulation, and neuronal apoptosis.[17] Moreover, interleukin (IL)-6 and IL-1β are markedly upregulated in brain tissue following radiotherapy,[18] and IL-6 has been shown to exacerbate radiation-induced cellular senescence in animal models.[19] The release of these inflammatory cytokines and activation of inflammatory pathways may damage neural cells, contributing to cognitive deficits.

Neuronal apoptosis and glial cell activation

Radiation induces cell death through both direct and indirect mechanisms. Direct damage involves DNA strand breaks caused by radiation, leading to cell death.[20] Indirect damage occurs via the generation of reactive oxygen species, resulting in DNA damage, impaired protein synthesis, and cell cycle arrest. This cascade leads to cellular swelling, necrosis, and further the production of reactive oxygen species, perpetuating inflammation and increased capillary permeability, ultimately culminating in irreversible radiation-induced brain necrosis.[21] These direct and indirect forms of damage reduce neural cell numbers, contributing to brain dysfunction within irradiated regions.

White matter injury and demyelination

White matter regions are rich in glial cells and neurons. Glial cells are more sensitive to radiation than neurons, and their gradual loss within white matter is considered a fundamental aspect of RIBI development.[22] As primary responders to central nervous system injury, microglia may promote astrocyte senescence. Research indicates that astrocytes preferentially undergo senescence after radiotherapy, while neural progenitor cells are more prone to apoptosis, suggesting that the secretory phenotype of senescent astrocytes may underlie chronic RIBI.[23] Radiation-induced white matter pathology disrupts neural signal transmission, leading to cognitive impairment and neurodegeneration.

Genetic susceptibility and RIBI

Beyond radiation and tumor-specific factors, individual radiosensitivity varies among patients. A genome-wide association study including nasopharyngeal carcinoma patients identified poly-

morphisms in the CEP128 promoter—such as rs17111237 and rs162171—as significantly associated with differential risk of temporal lobe radiation-induced injury (hazard ratios ~1.45–1.46, $P < 10^{-7}$).[24] This represents the first study implicating CEP128 in RIBI, offering new insights into potential mechanisms.

Treatment-related factors

RIBI risk is influenced by radiotherapy modality, total dose, fractionation schemes, and the concurrent use of chemotherapy, targeted therapy, or immunotherapy. Advances in techniques such as intensity-modulated radiotherapy, stereotactic radiosurgery (SRS), and image-guided radiotherapy have improved precision, reduced exposure to surrounding normal tissues, and decreased RIBI risk.[25]

Studies from the Radiation Therapy Oncology Group have shown a positive correlation between RIBI risk and total radiation dose.[26] For example, in patients with high-grade gliomas treated with SRS, the incidence of RIBI is approximately 6.5%. When total doses range between 18 and 30 Gy, incidence varies from 4.7% to 9.2%, with higher doses associated with greater risk.

Tumor size also influences RIBI risk, with larger tumors correlating with higher incidence following SRS (2.9–22.6%).[27] Radiation-induced cognitive impairment is related to the structure and dose thresholds of irradiated targets. Localized brain irradiation may not cause cognitive deficits of the same magnitude as whole-brain irradiation.[28,29] Selective damage to critical brain structures, such as the hippocampus and temporal lobes, may underlie post-radiotherapy cognitive dysfunction; preserving these regions can help maintain cognitive function.

The impact of combined therapies on RIBI remains under investigation. While some retrospective studies suggest agents such as bevacizumab and immune checkpoint inhibitors do not increase RIBI incidence, further research is needed to validate these findings.[30,31] With continued advances in radiotherapy techniques, improved treatment planning, and the development of pharmacological interventions, the incidence of RIBI is expected to further decline.

Clinical manifestations of RIBI

RIBI is typically categorized into three phases based on onset time and pathological progression: acute, subacute (early-delayed), and late-delayed phases.[32]

Acute phase (within hours to weeks post-radiotherapy)

This phase is primarily characterized by symptoms indicative of increased intracranial pressure, including headache, nausea, vomiting, and somnolence. These manifestations are often attributed to reversible cerebral edema and are relatively uncommon in clinical practice. The underlying pathophysiology involves disruption of the BBB and alterations in capillary permeability, leading to vasogenic edema.

Subacute phase (one to six months post-radiotherapy)

During this phase, patients may experience transient cognitive impairments, somnolence, emotional fluctuations, and mild memory decline. Neuroimaging frequently reveals diffuse white matter signal changes. While some cases resolve spontaneously, others may progress to late-delayed brain injury. The pathogenesis is thought to involve transient demyelination and oligodendrocyte dysfunction, potentially linked to BBB disruption.

Late-delayed phase (beyond six months post-radiotherapy)

This phase represents the most common and severe form of RIBI. Clinical features include progressive cognitive decline, disorientation, language and executive function deficits, and, in severe cases, seizures, psychiatric disturbances, coma, or death. Neuroimaging findings often demonstrate brain atrophy, necrotic lesions, and progressive white matter changes. The underlying mechanisms are multifactorial, involving vascular abnormalities, demyelination, and white matter necrosis.

The risk of developing RIBI is influenced by various factors, including radiation dose and fractionation schedule, irradiated brain volume, patient age, comorbid conditions (such as hypertension and diabetes), and concurrent systemic chemotherapy. Accurate recognition of the clinical features and an understanding of the pathophysiological mechanisms are crucial for early detection, differential diagnosis, and precise management of RIBI.

Advances in multimodal imaging for the diagnosis of RIBI

Advanced MRI technology

RIBI is challenging to detect early due to its insidious onset and non-specific clinical symptoms. Moreover, distinguishing its imaging features from tumor recurrence remains difficult using a single modality. In recent years, multimodal imaging strategies centered on MRI, integrating structural, functional, metabolic, perfusion, and artificial intelligence analyses, have emerged as crucial approaches for the precise assessment of RIBI (Table 1).

Within MRI sequences, T1-weighted imaging, T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) are highly sensitive in detecting parenchymal abnormalities, white matter lesions, necrotic foci, and brain atrophy. FLAIR is particularly sensitive to white matter demyelination, often presenting as hyperintense areas within or at the margins of the irradiated field.[33]

Diffusion imaging techniques reflect the diffusion state of water molecules within tissues. Diffusion-weighted imaging (DWI) can evaluate cellular density and regions with restricted water diffusion, aiding in differentiating hypercellular tumor areas from necrotic tissue. DWI provides apparent diffusion coefficient (ADC) values, also referred to as mean diffusivity. Rapid tumor cell proliferation increases cellular density in lesions, leading to decreased ADC values. In contrast, neuronal necrosis following RIBI reduces cellular density, resulting in increased ADC values.[34] Diffusion imaging enables the assessment of microstructural changes in brain tissue. Integration of relative cerebral blood volume (CBV) and K^{trans} has achieved diagnostic accuracy exceeding 90% in glioblastoma follow-up.[35]

Diffusion tensor imaging offers additional parameters, including fractional anisotropy,[36,37] axial diffusivity, and radial diffusivity. Several studies have focused on microstructural changes in white matter following radiotherapy, showing decreased fractional anisotropy, increased mean diffusivity,[38,39] and elevated radial diffusivity,[38,40,41] primarily attributed to demyelination or axonal loss.[42,43] Perfusion imaging techniques, by measuring cerebral blood flow and CBV, help differentiate pathological conditions. Studies have shown that regions of radiation necrosis often exhibit hypoperfusion (low cerebral blood flow/CBV), whereas tumor recurrence typically shows hyperperfusion. Among these techniques, arterial spin labeling (ASL) does not require contrast agents and is suitable for repeated monitoring, while dynamic contrast-enhanced (DCE) and dynamic susceptibility contrast (DSC) perfusion imaging provide vascular permeability and perfusion curves, offering high sensitivity in assessing post-radiotherapy lesion activity. Perfusion-weighted imaging (PWI) can detect radiation-induced

Table 1. Comparison of multimodal imaging technologies

Multimodal imaging	Principle	Applications	Pros and Cons
FLAIR	Suppressing cerebrospinal fluid (CSF) signal to highlight abnormal tissue	Detecting parenchymal abnormalities	Highly sensitive to white matter demyelination
DWI	Measuring water molecular diffusion	Differentiating hypercellular tumors, radiation necrosis	Provides apparent diffusion coefficient (ADC) values
DTI	Analyzing the diffusion of water molecules along axonal fibers	Assessing white matter microstructure	Useful for detecting demyelination and axonal loss; Limitation in crossing fiber evaluation
PWI	Evaluating cerebral perfusion	Monitoring cerebral perfusion	Need for contrast agents: Sensitivity to artifacts. Contrast agents; Longer scan time
MRS	Quantifying brain metabolite concentration	Quantifying radiation-induced neurotoxicity	Provides non-invasive functional imaging
BOLD	Based on blood oxygenation level-dependent	Assessing brain function and hemodynamic	Provides non-invasive functional imaging

BOLD, blood oxygen level–dependent imaging; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRS, magnetic resonance spectroscopy; PWI, perfusion-weighted imaging.

vascular changes; most PWI studies report reduced perfusion and decreased CBV following radiotherapy.[44,45] A combination of PWI and DWI improves diagnostic performance and can obviate unnecessary biopsies in approximately 10% of cases.[46] Common MRI perfusion techniques in clinical practice include DSC, DCE, and ASL, each with specific advantages and limitations. DSC, based on T2-weighted imaging following rapid contrast injection, effectively reflects tumor perfusion but is prone to artifacts from metal, blood, and air. DCE, based on T1-weighted contrast-enhanced imaging, is less artifact-prone but requires advanced post-processing software, limiting widespread use. ASL does not require gadolinium injection but has lower spatial resolution, which can limit clinical utility.

Additionally, susceptibility-weighted imaging (SWI) has been used to observe microbleeds and assess radiation-induced microvascular changes. Peters *et al*.[47] found that children develop punctate SWI lesions more rapidly and earlier than adults. In a longitudinal study of pediatric patients treated for brain tumors with proton therapy, the cumulative incidence of radiation-induced cerebral microbleeds, as detected by SWI, increased progressively over time—reaching 43% at one year and 83% by five years post-therapy. The occurrence of cerebral microbleeds correlated significantly with higher radiation doses, greater irradiated brain volume, and younger age at treatment ($p < 0.01$).[48] MRS is a non-anatomical imaging technique that quantifies metabolite concentrations within specific brain regions. MRS enables non-invasive detection of metabolic changes, allowing potential quantification of radiation-induced neurotoxicity. In the healthy brain, metabolites such as N-acetylaspartate and choline show distinct peaks.[49] Among 242 patients who underwent both MRS and PET-computed tomography (CT) examinations, the diagnostic accuracy of MRS was 81.8%, significantly higher than that of PET-CT (42.9%).[50] Changes in neuronal and glial cell populations alter intracranial metabolite concentrations.[51] The N-acetylaspartate/creatine ratio is higher in regions of radiation necrosis than in tumor regions, while choline/N-acetylaspartate and choline/creatine ratios are higher in recurrent tumors. Reduced choline levels, along with potentially elevated lipid and lactate signals, suggest radiation necrosis.[52] However, the long scan times required for accurate assessment limit the routine clinical use of MRS.

Deoxyhemoglobin is more paramagnetic than oxyhemoglobin, serving as a natural contrast agent. When vascular damage following radiotherapy causes imbalances between oxygen uptake and cerebral circulation, MRI sequences sensitive to magnetic field inhomogeneity can detect signal changes around cortical vessels. This is known as blood oxygenation level-dependent (BOLD) contrast. BOLD allows functional localization studies without contrast agents while providing high spatial resolution. Signal changes theoretically depend on intracranial blood oxygenation, blood flow, hematocrit, and tissue oxygen uptake, with blood flow being the primary determinant. BOLD functional MRI includes task-based and resting-state fMRI. Due to its ability to non-invasively measure hemodynamic changes, BOLD fMRI enables assessment of local neuronal and synaptic activity and, with high spatial and temporal resolution, has been widely used in neurological, psychiatric, and psychological research.[53,54] This technique may also be applicable for detecting RIBI.

In cases of cerebral radiation necrosis, conventional MRI typically shows ring-enhancing lesions at the treatment site with surrounding edema, which are non-specific and may also occur in tumor progression.[55] Diagnostic uncertainty for radiation necrosis based on conventional imaging alone can reach up to 15%.[56] With the increasing use of immunotherapy, this uncertainty is further heightened, as pseudoprogression related to immune responses is often indistinguishable from true tumor progression using contrast-enhanced MRI alone.[55] Therefore, additional imaging modalities are needed to supplement conventional methods for accurate evaluation. Based on the above content and previous studies, we summarized the general diagnostic and treatment workflow for MRI in RIBI (Fig. 2).

Application of PET/CT and single photon emission computed tomography (SPECT) in the evaluation of RIBI

PET imaging can reveal the metabolic and inflammatory status within radiotherapy-treated regions and serves as a critical adjunct in the assessment of RIBI. PET/CT differentiates tissues based on varying uptake of radiolabeled glucose (fluorodeoxyglucose (FDG)). Tissues with higher glucose metabolism demonstrate increased FDG uptake, while necrotic tissues show reduced glucose metabolism and consequently decreased FDG uptake. Most tumor tissues have elevated glucose metabolism and thus higher FDG

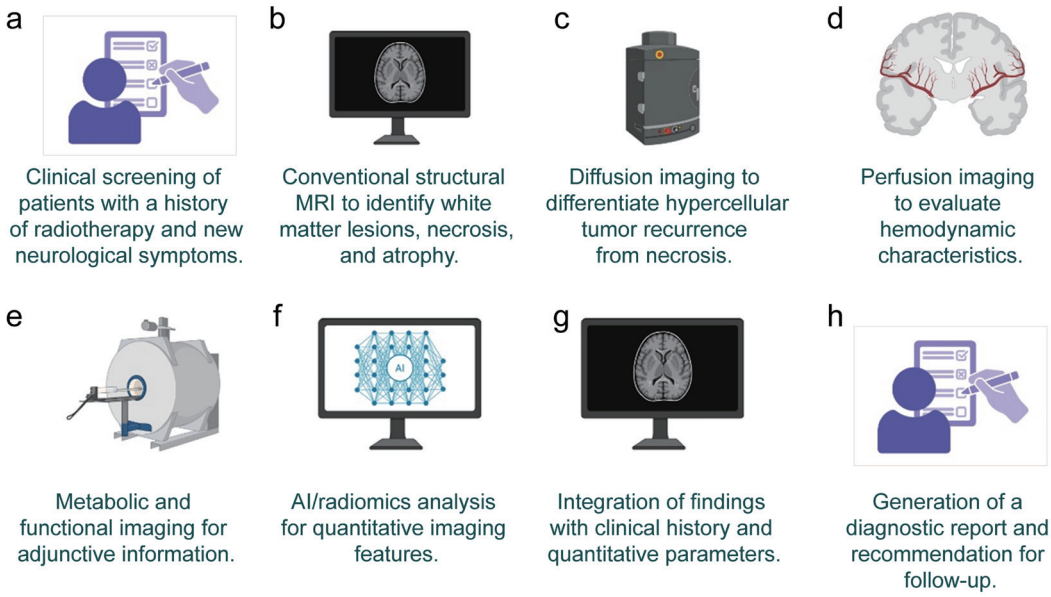

Fig. 2. MRI diagnostic imaging workflow for RIBI. (a) The workflow begins with clinical screening in patients with a history of radiotherapy and new neurological symptoms, excluding acute metabolic or vascular events. (b) Conventional structural MRI (T1WI, T2WI, FLAIR) identifies white matter lesions, necrosis, and atrophy, with FLAIR being particularly sensitive for detecting demyelination. (c) Diffusion imaging (DWI, ADC, MD) aids in differentiating hypercellular tumor recurrence from necrosis, while DTI (FA, AD, RD) assesses demyelination and axonal loss. (d) Perfusion imaging (PWI: CBV, CBF; ASL; DCE; DSC) evaluates hemodynamic characteristics, distinguishing low perfusion in necrosis from hyperperfusion in recurrence. (e) Metabolic and functional imaging (MRS for NAA, Cho, Lac, Lip; SWI for microbleeds; BOLD-fMRI) provides adjunctive information. If available, (f) AI/radiomics analysis offers quantitative imaging features to assist in differentiating necrosis from tumor recurrence. Finally, findings are (g) integrated with clinical history and (h) quantitative parameters to generate a diagnostic report, with follow-up recommended for monitoring dynamic changes when necessary. AD, axial diffusivity; AI, artificial intelligence; ASL, arterial spin labeling; BOLD-fMRI, blood oxygen level–dependent functional magnetic resonance imaging; CBF, cerebral blood flow; CBV, cerebral blood volume; DCE, dynamic contrast-enhanced (MRI); DSC, dynamic susceptibility contrast (MRI); DTI, diffusion tensor imaging; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; PWI, perfusion-weighted imaging; RD, radial diffusivity; RIBI, radiation-induced brain injury; SWI, susceptibility-weighted imaging; T1WI, T1-weighted imaging.

uptake. SPECT provides three-dimensional images of the target organ through multi-angle scanning. Various radiotracers are available for SPECT imaging; however, compared to MRI and PET/CT, SPECT has disadvantages including relatively lower spatial resolution, higher radiation dose, and slower scanning speed.[57] Commonly used tracers include:

- *18F-FDG*, which reflects glucose metabolism but has limited discriminatory ability due to high background metabolic activity in brain tissue[58];
- *18F-DPA714*, which targets the translocator protein and can identify microglial activation, represents a novel method for assessing inflammatory status. Translocator protein PET has been widely used in recent years to explore neuroinflammatory mechanisms in RIBI, providing imaging support for targeted therapies.[59]

However, the use of radiolabeled glucose has limitations. For example, some low-grade intracranial tumors have low FDG uptake, leading to false-negative results in clinical practice. Therefore, exploration of additional tracers is necessary to improve differentiation of RIBI.

Radiomics and artificial intelligence analysis

In recent years, radiomics combined with machine learning has emerged as a forefront approach for diagnosing RIBI. By extracting high-dimensional quantitative imaging features (such as intensity, texture, and shape), classification models are established to assist in distinguishing tumor recurrence from radiation necrosis. In 2023, Salari *et al*.[60] constructed a random forest model based on T1+C and FLAIR sequence images, achieving over 90% classification accuracy in the validation cohort, providing technical support for noninvasive and automated diagnosis of RIBI. Moreover, deep learning models have shown promising prospects in predicting and dynamically evaluating RIBI.

The integration of multimodal imaging technology has allowed the assessment of RIBI to evolve from traditional structural evaluation toward comprehensive analysis encompassing function, metabolism, microstructure, and inflammatory status. Each imaging modality possesses distinct advantages, and their rational combined application facilitates earlier detection, improved differential diagnosis, and precise guidance for clinical intervention strategies.

Treatment of RIBI

RIBI currently lacks standardized treatment guidelines, with clinical management mainly consisting of symptomatic support and empirical interventions. With increasing understanding of its pathogenesis, therapeutic strategies have gradually expanded from traditional glucocorticoid-based approaches to multi-target comprehensive treatments addressing vascular leakage inhibition, neuroinflammation suppression, neural repair promotion, and gut-brain axis modulation. The following section reviews recent advances in RIBI treatment from the perspectives of pharmacotherapy, neuromodulation techniques, and systemic interventions (Table 2).[61–67]

Table 2. Treatment strategies for radiation-induced brain injury

Treatment	Mechanism	Evidence level	Indications	Advantages	Limitations/ adverse effects	References
Bevacizumab	Inhibits VEGF, reduces angiogenesis and vascular permeability, improves imaging enhancement and edema	RCT (Level I)	Symptomatic radiation necrosis with edema	Rapid symptom relief; reduces steroid dependence	High cost; potential hypertension and bleeding risk	Levin *et al*., 2011[61]
Corticosteroids (dexamethasone)	Inhibit the release of inflammatory mediators, restore BBB integrity, alleviate edema	Clinical observation (Level II-III)	Acute phase of radiation-induced brain edema; symptomatic relief	Rapid onset; widely accessible	Long-term use associated with significant adverse effects (osteoporosis, infections)	Meixner *et al*., 2023[62]
Hyperbaric oxygen (HBO)	Provides high-pressure oxygen to promote neovascularization and repair	Small cohort/ animal studies (Level III)	Early-stage radiation-induced injury or refractory cases with edema	Potential prophylactic benefit; non-systemic toxicity	Lack of large-scale RCTs; resource-intensive	Hajikarimloo *et al*., 2024[63]
Mesenchymal stem cells (MSCs)	Suppress microglial pyroptosis and inflammation, secrete neurotrophic factors, promote repair	Animal models (Level III)	Experimental therapy for chronic radiation-induced brain injury	Multi-target regulation; improves cognition and tissue structure	Difficulties with autologous transplantation; mechanisms remain unclear; no human trials	Pan *et al*., 2025[64]
Endothelial progenitor cells (EPCs)	Participate in endothelial repair, re-endothelialization, and angiogenesis	Mouse/*in vitro* studies (Level III)	Preclinical use for vascular damage after irradiation	Specific action; stabilizes BBB	Isolation and purification challenges; low transplantation efficiency	Goksu *et al*., 2024[65]
TSPO inhibitors (e.g., XBD173, PK11195)	Target microglial activation, suppress neuroinflammation; dual role in diagnosis and therapy	Animal studies (Level III)	Imaging and potential treatment of neuroinflammation in radiation-induced injury	Small molecules; easy delivery; allows imaging tracking	Limited clinical validation; potential unknown adverse effects	Zhang *et al*., 2023[66]
Gut-brain axis interventions (probiotics/FMT)	Modulate gut microbiota to reduce central inflammation and cognitive dysfunction	Animal studies (Level III)	Exploratory therapy for chronic cognitive impairment post-radiation	Non-invasive; easily scalable	Complex mechanisms; lacks human validation	Luo *et al*., 2022[67]

BBB, blood–brain barrier; FMT, fecal microbiota transplantation; RCT, randomized controlled trial; TSPO, translocator protein (18 kDa); VEGF, vascular endothelial growth factor.

Pharmacological treatment

Bevacizumab is the only treatment demonstrated to be effective against cerebral radiation necrosis in randomized controlled trials.[68] Preclinical studies have shown that intra-arterial administration of bevacizumab can successfully treat cerebral radiation necrosis, with effects lasting up to 8.5 months post-treatment. Pan *et al*.[69] reported that bevacizumab relieved clinical symptoms in over 70% of RIBI patients, with MRI demonstrating improved perfusion and lesion shrinkage.

Corticosteroids are the first-line drugs for treating cerebral radiation necrosis. Steroids inhibit the release of cytokines and inflammatory mediators from necrotic tissue, reducing cytokine-induced inflammatory responses while improving BBB integrity and alleviating cerebral edema. Dexamethasone is commonly prescribed for RIBI. Short-term corticosteroid use can effectively reduce symptoms of cerebral radiation necrosis.[70] However, clinicians should be alert to adverse effects associated with long-term use, and alternative treatment options need to be explored.

Sildenafil and simvastatin exhibit antioxidant and anti-inflammatory properties, acting respectively as nitric oxide donors and Tetrahydrobiopterin (BH4) regulators. Combined administration of sildenafil and simvastatin modulates the indoleamine 2,3-dioxygenase/kynurenine pathway through nitric oxide donor/BH4 regulatory activity, exerting anti-inflammatory and antioxidant effects, and provides neuroprotection against RIBI.[71]

Preclinical studies have explored the use of anticoagulants (hepa-

rin, warfarin),[72] pentoxifylline,[73] and metformin for RIBI management.[74] These agents act through mechanisms including improving microcirculation, reducing fibrosis, promoting neuronal survival, and attenuating neuroinflammation. However, further studies are needed to confirm their safety and efficacy in clinical settings.

Hyperbaric oxygen therapy

Most case reports show improvement of radiation necrosis symptoms with hyperbaric oxygen (HBO) therapy, which also reduces corticosteroid usage.[75] HBO effects have been observed to persist for extended periods[76]; however, randomized clinical trial data are lacking.

The basic principle of HBO in treating RIBI is that increased oxygen concentration stimulates angiogenesis, restoring blood supply to necrotic lesions and facilitating repair. Patients undergo treatment in a chamber at 2.5 atmospheres absolute, receiving 100% oxygen up to five times per week, with treatment cycles repeated up to 40 sessions. Studies indicate that prophylactic HBO after 20 sessions of SRS can reduce the incidence of brain radiation necrosis from 20% to 11% within one week post-treatment.[77] Nonetheless, no prospective randomized controlled trials have definitively confirmed HBO's therapeutic efficacy in RIBI.

Stem cell therapy

Preclinical studies indicate that mesenchymal stem cells contribute to vascular system repair in various organs and tissues. Strong evidence supports the role of endothelial progenitor cells in re-endothelialization, angiogenesis, and endothelial repair.[78] Other studies report that transplanted bone marrow stem cells influence cytokine secretion,[78] monocyte maturation and/or recruitment, and macrophage migration to injury sites,[79] which may impede tissue repair. These findings warrant further investigation into the roles of endothelial progenitor cells and transplanted mesenchymal stem cells in vascular recovery.

Post-radiotherapy reductions in pericyte populations have been observed and may contribute to cognitive dysfunction. Pericytes are a heterogeneous group of mural cells associated with microvasculature and play critical roles in endothelial proliferation, BBB integrity, capillary constriction, and blood flow regulation.[80,81] Mesenchymal stem cells differentiate into cell types constituting the neurovascular unit, including pericytes. Therefore, recruitment of bone marrow-derived pericytes to the brain following chronic systemic hypoxia requires further exploration. Extensive research is still needed to elucidate the reparative potential of mesenchymal stem cells in RIBI.

Biological therapy

Some researchers have identified astrocyte senescence and astrocyte-derived neuroinflammation as potential triggers of RIBI. For example, studies on Δ133p53 have shown that Δ133p53 inhibits full-length p53 and modulates factors such as p21 and IL-6,[82–84] suppressing inflammatory processes. These inflammatory mediators have been implicated in radiation injury and neurotoxicity. Although the interactive mechanisms among these factors are not fully elucidated, findings suggest that preventing astrocyte senescence and inhibiting astrocyte-mediated neuroinflammation by inducing the p53 isoform Δ133p53 may hold therapeutic potential.[82]

Neuromodulation and rehabilitation interventions

Neuromodulation techniques are emerging as important non-pharmacological interventions for cognitive impairment and emotional disturbances in RIBI.[83,84]

- *Transcranial magnetic stimulation:* Low-frequency repetitive transcranial magnetic stimulation has been applied in post-stroke cognitive rehabilitation, with preliminary studies showing improvements in attention and executive function in RIBI patients and demonstrating good safety profiles.[85]
- *Functional MRI neurofeedback:* Training patients to regulate their own brain activity and enhance activation in specific brain regions has shown potential when combined with cognitive training and radiotherapy rehabilitation.[86]

Gut-brain axis-based intervention strategies

The gut-brain axis refers to the bidirectional communication network between the gut and the brain, serving as a key pathway linking the gut microbiota with neurological function.[87]

Recent studies have found that radiotherapy alters gut microbiota composition, influencing brain inflammation and neurological function, suggesting a potential role of the gut-brain axis in RIBI pathogenesis.[88] In irradiated mouse models, gut dysbiosis is significant and accompanied by cognitive impairment and excessive microglial activation.[89] Fecal microbiota transplantation and probiotic interventions partially reverse neural damage in animal experiments, indicating a promising therapeutic direction.[90] Numerous studies have demonstrated a close association between the gut microbiota and various neurological disorders, including Alzheimer's disease, traumatic brain injury, and Parkinson's disease. Interventions targeting the gut microbiota have shown potential in altering the progression of these conditions. Therefore, the gut microbiota represents a promising therapeutic target for neurological diseases. In patients undergoing intracranial radiotherapy, disruption of the BBB increases the likelihood that gut microbiota and its metabolites may influence the nervous system. Although treatment strategies for RIBI are still under investigation, targeted modulation of the gut microbiota offers a novel therapeutic avenue.

Challenges and future research directions

Despite significant advances in the imaging diagnosis and treatment of RIBI in recent years, its clinical management still faces numerous challenges that require breakthroughs in the following areas:

Lack of unified diagnostic criteria and imaging specificity

Currently, the diagnosis of RIBI relies primarily on a combination of imaging findings and clinical experience, with no standardized diagnostic workflow or grading system established. Conventional MRI often has considerable limitations in detecting early lesion changes and differentiating them from tumor recurrence. Although multimodal imaging shows promise in improving diagnostic accuracy, its clinical application is hindered by complex image fusion processes, lack of unified technical standards, and high dependency on subjective interpretation.

Furthermore, data integration across different imaging modalities lacks a unified platform. In particular, the generalizability and clinical interpretability of radiomics and machine learning models in artificial intelligence-assisted diagnosis remain inadequate.

Limited therapeutic options and lack of mechanism-driven interventions

Current RIBI treatments mainly focus on glucocorticoids and symptomatic management, with few interventions targeting the underlying pathological mechanisms. Although bevacizumab can alleviate symptoms in the short term, its long-term efficacy and safety re-

quire validation in large-scale studies. Emerging strategies, including anti-inflammatory, antioxidant, neurotrophic, and gut-brain axis interventions, are mostly at the experimental stage, without an established, systematic evidence-based therapeutic framework.

Absence of early biomarkers and risk prediction models

The irreversible nature of RIBI underscores the importance of early identification and intervention. However, reliable predictive indicators and sensitive molecular imaging biomarkers are still lacking. Developing individualized risk prediction models by integrating clinical, imaging, blood-based, and genetic data represents a critical direction for future preventive intervention research.

Insufficient interdisciplinary collaborative research

RIBI involves multiple disciplines, including radiotherapy physics, neuroimaging, neurobiology, and clinical neuroscience. Current research is characterized by fragmented efforts with limited multi-center, large-sample, interdisciplinary collaboration, impeding the integrated advancement of mechanistic understanding, imaging techniques, and therapeutic interventions.

Future research directions

To address these shortcomings, future efforts should focus on: (1) *Defining diagnostic standards:* Establish consensus RIBI grading frameworks and integrate multimodal imaging data into interoperable workflows. (2) *Targeting pathophysiology:* Advance research on agents that modulate microglial activation or oxidative injury, such as RAS inhibitors that attenuate neuroinflammation in preclinical models.[1] (3) *Identifying predictive biomarkers:* Validate blood and neuroimaging indicators of early RIBI risk (e.g., IL-1β, tumor necrosis factor-α, glial fibrillary acidic protein) and develop multivariable predictive models incorporating clinical, molecular, and imaging data. (4) *Fostering multidisciplinary, multicenter research:* Encourage collaborative networks that unify preclinical mechanistic insights, standardized imaging protocols, and therapeutic trials to translate findings into clinical practice.

Conclusions

RIBI remains a significant late complication of cranial radiotherapy, impacting cognition and quality of life. It is regarded as a complex and pressing complication in neuro-oncology, presenting persistent challenges in diagnosis and management. Multimodal imaging, including structural MRI, diffusion-based modalities, perfusion imaging, MRS/PET, and artificial intelligence-driven radiomics, has significantly enhanced early detection and differentiation of RIBI from tumor recurrence. However, most therapeutic strategies, including corticosteroids, bevacizumab, and experimental agents, remain largely palliative and lack high-level evidence for long-term benefit. Future efforts should focus on standardizing imaging workflows, developing validated predictive biomarkers, and conducting rigorous clinical trials of neuroprotective and neuromodulatory therapies to enable precision management of RIBI.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Study concept and design (XC), manuscript writing (XW, SL), data analysis (XW, FY). All authors approved the manuscript prior to submission.

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