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Review

# Cerebral radiation necrosis: A review of the pathobiology, diagnosis and management considerations

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ABSTRACT

Radiation therapy forms one of the building blocks of the multi-disciplinary management of patients with brain tumors. Improved survival following radiation therapy may come with a cost, including the potential complication of radiation necrosis. Radiation necrosis impacts the quality of life in cancer survivors, and it is essential to detect and effectively treat this entity as early as possible.

Significant progress in neuro-radiology and molecular pathology facilitate more straightforward diagnosis and characterization of cerebral radiation necrosis. Several therapeutic interventions, both medical and surgical, may halt the progression of radiation necrosis and diminish or abrogate its clinical manifestations, but there are still no definitive guidelines to follow explicitly that guide treatment of radiation necrosis. We discuss the pathobiology, clinical features, diagnosis, available treatment modalities, and outcomes in the management of patients with intracranial radiation necrosis that follows radiation used to treat brain tumors.



## Introduction

Conventional radiation therapy (CRT) and stereotactic radiation therapy (SRT) represent important components of comprehensive strategies to treat patients with brain tumors. Three time-limited forms of radiation toxicity have been described: acute, early delayed and delayed long-term radiation-induced neurotoxicity. Acute toxicity occurs during or immediately after radiation treatment; early delayed neurotoxicity occurs up to 12 weeks following treatment; and delayed neurotoxicity develops and evolves from 3 months to a few years following treatment (Fig. 1).[1] The various manifestations of delayed radiation neurotoxicity include radiation necrosis (RN), radiation leukoencephalopathy, radiation myelopathy, and, in the peripheral nervous system, plexus or nerve root lesions.[2,3] In 1930, Fischer and Holfelder described the first case of delayed RN following radiation therapy of a basal cell carcinoma of the scalp.[4] In 1950, Lowenberg-Scharenberg described the pathological occurrence of amyloid degeneration in cerebral parenchyma following X-ray irradiation.[5] These initial descriptions were followed by numerous additional reports, series and reviews that have since documented RN as a major complication of therapeutic central nervous system (CNS) irradiation.[6–11] Similar effects have also been observed as a complication of radiation therapy to tumors of the paranasal sinuses, nasopharynx, middle ear, parotid and lacrimal glands, in which cases the CNS is incidentally involved in the treatment field(s).[12,13]

The exact incidence of intracranial RN remains undetermined, although it ranges from 5–50%, depending on the modality of treatment, the dose delivered, the duration a patient is followed clinically and with neuroimaging, the neuroimaging criteria used, and whether clinical signs and symptoms are present.[14] Kramer et al. initially attempted to determine the incidence of RN by reviewing the literature, but could not come to a conclusion because of a lack of data regarding the total treated population.[15] Several factors continue to complicate a detailed analysis of the actual rates of RN, including alternate modalities of radiation therapy, the fact that the published literature comprising mostly class III evidence, that not all reported studies have histopathological confirmation of their findings, and that variable treatment parameters have been used for radiation delivery (including dose, fractionation schedules, treatment times, radiation field arrangements and volume).[9] Additionally, most of the studies took place prior to the availability of modern neuro-imaging, making it difficult to calculate radiation parameters.[9,16,17] The use of adjuvant chemotherapy has further confounded the analysis of data. In addition, the exact population being diagnosed and treated has also been variably reported in the literature as the number of patients treated rather than those at risk (survivors), which may underestimate risk, thus making it difficult to ascertain a precise incidence for RN.

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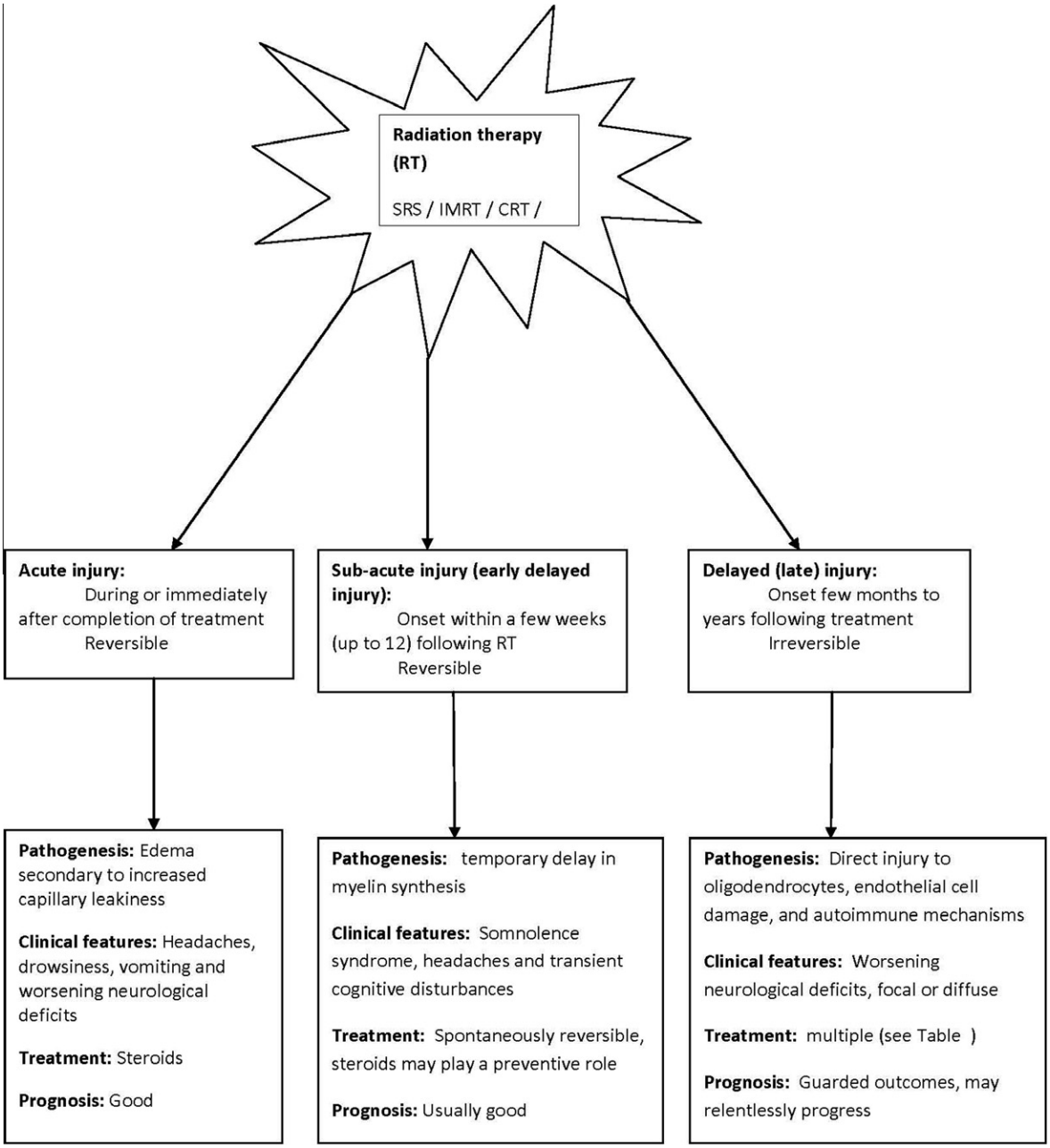


**Fig. 1.** An algorithm for the classification of cerebral radiation therapy toxicity based on the time interval since treatment. SRS = stereotactic radiosurgery, IMRT = intensity modulated radiation therapy, CRT = conventional radiation therapy.

In this review we present a comprehensive review of intracranial RN after therapeutic brain irradiation, with a focus on RN developing in patients after radiation therapy of a brain tumor. We discuss the pathobiology of RN, its clinical features, its diagnosis, and potential strategies for its management, including the benefit and toxicity profiles of these therapies.

## Pathobiology of radiation necrosis

Radiation-induced damage can occur with radiation doses as low as 50 Gy, however the radiation dose is directly proportional to the risk of brain injury.[18] In cases where fractionated therapy is used, larger fractional doses correspond to a greater risk of subsequent RN.[19] Chemotherapy may potentiate the risk of brain injury, and was first reported in children who survived treatment for leukemia.[20] Lai et al. reported a series of five patients, treated with whole brain radiotherapy and high-dose methotrexate, who died from treatment-related leukoencephalopathy.[21] Burger et al. describe encephalopathy in four patients treated with high-dose I,3-Bis-(2-chloroethyl)-l-nitrosourea(BCNU),[22] with necropsy revealing large, symmetric foci of vascular changes with fibrinoid necrosis and fibrin thrombi. These findings were similar to those of methotrexate-induced toxicity.[23] Additional reports describing adverse effects with combined radiation and chemotherapy have been reported in patients with leukemia,[24] gliomas,[25] bone or soft tissue sarcoma[26] and small cell carcinoma of the lung.[27]

Two models have been proposed to explain cerebral RN: the vascular injury theory and the glial injury theory. Since neither can individually explain the changes occurring in RN, it is likely that a combination of these (and, potentially, additional) mechanisms plays a role in the complex pathogenesis of RN (Fig. 2).[9]