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CLINICAL INVESTIGATION

Contrast-enhancing Lesions Induced by Central Nervous System-directed Intensity Modulated Proton Therapy: Distribution Patterns, Kinetics, Risk Factors, and Outcomes

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Purpose

Patients treated with intensity modulated proton therapy (IMPT) may develop intracranial radiation-induced contrast enhancement (RICE). The incidence, distribution, kinetics, predisposing factors, linear energy of transfer (LET) associations, and clinical outcomes of RICE are inadequately defined.

Methods and Materials

The incidence and characteristics of RICE were analyzed in brain tumor patients treated with at least 50 Gy IMPT, 1-year follow-up, and 3 posttreatment magnetic resonance imaging scans. RICE distribution was classified as overlapping with tumor/tumor bed (A), inside or marginal to high-dose region (≤5 mm from the 95% isodose line [IDL]) (B), or distant (>5 mm from 95% IDL) (C). Voxelized dose and LET were computed for each RICE lesion. Risk factors were assessed using binary logistic regression.

Results

With a median follow-up of 3 years, 73 RICE lesions were observed in 36 of 137 patients (26%), appearing at a median of 11 months post-IMPT. Group-wise distribution demonstrated 10 (28%), 24 (67%), and 2 (5%) lesions in groups A, B, and C, respectively. Ten (7% overall) patients were symptomatic. After a median of 5 months, most lesions (78%) improved or resolved. Median dose and LET in RICE lesions were 50.4 Gy and 3.1 keV/μm. RICE risk increased with age as a continuous variable (0.4%/year), age ≥18 years (odds ratio [OR], 5.4), tumor volume >30 cc (OR, 2.8), and 95% IDL overlapping the ventricles (OR, 3.8).

Conclusions

RICE is a common radiographic finding after IMPT, primarily occurring in the periventricular and high-dose regions, but is infrequently symptomatic. Periventricular-sparing treatment may be considered to minimize the risk of RICE.

Introduction

Radiation therapy (RT) is one of the key modalities for managing both benign and malignant primary central nervous system (CNS) tumors, either as part of a multimodality approach, or as a single, and often curative, treatment.[1] The number of patients with CNS tumors treated with proton therapy is increasing,[2] owing to significant dosimetric advantages compared with photon RT[3] and increasing availability of and access to particle therapy centers.[4]

Exposure of normal brain to some radiation dose is inevitable even when using contemporary highly conformal intensity modulated proton therapy (IMPT).[5] This can elicit a diverse and complex tissue response. Involved molecular mechanisms are speculated to include chronic neuroinflammation, destruction of the blood-brain barrier, oxidative stress, neuronal damage, and responses caused by specific exosome secretion.[6] These processes may result in disruption or injury of normal tissue, often superimposed on or adjacent to the underlying neoplastic lesion and may appear as contrast-enhancing lesions on routine follow-up magnetic resonance imaging (MRIs), with or without associated symptoms. Over time, overlapping phrases were coined to describe similar phenomena, based on timing, presumed pathologic process (radiation necrosis), tumor response (pseudoprogression), or MRI changes (radiation-induced contrast enhancement [RICE]).[7] The constellation of these postradiation changes remain inadequately defined with an incidence ranging from 0.6% to 34% in modern proton RT series.8, 9, 10

Although the exact mechanisms underlying RICE development remains unknown, multiple risk factors were suggested. These include patient dependent factors (such as age and cardiovascular comorbidities),[11,12] tumor-related characteristics (such as histology and location),[13,14] treatment-related factors (such as dose, beam arrangement, spot weight, and radiobiological considerations involving the known higher relative biological effectiveness [RBE] at the end of range of a proton beam, consequential to higher linear energy of transfer [LET]).[15]

Our study investigates the spatial distribution patterns of RICE lesions, hypothesizing a causal link between their location and the gross tumor volume (GTV), as well as their anatomic propensity to specific brain regions. Additionally, we analyze the temporal kinetics of RICE, corresponding patient-related risk factors, and clinical outcomes, to understand potential differences based on type and classification of RICE.

Section snippets

Data acquisition and patient eligibility

After institutional review board approval (December 27, 2023; protocol number 2023-RETRO-YU-001), patients treated at a single tertiary care institution between 2017 and 2023 with IMPT for primary CNS tumors were queried. Before selection for proton therapy, all cases were discussed in dedicated peer review sessions and selected if deemed suitable for proton therapy based on available evidence.[4,16] Key inclusion criteria were a minimum of 1 year follow-up, 3 posttreatment MRI scans, and at …

Results

The study cohort included 137 patients out of 457 treated with IMPT for both malignant and benign CNS tumors during the study period (Fig. E1). Patient, tumor, and treatment characteristics are listed in detail in Table 1. The median age was 40 years (range, 1-85), 51% were female and 53% Hispanic. Most patients had a Karnofsky performance status of 90 to 100 (115, 84%). The most common histologies were meningioma (32, 23%) and high-grade glioma (31 total, 23%; 16 World Health Organization …

Discussion

Increasing use of proton therapy during the last decade has led to an increasing focus on normal tissue response and adverse effects of this modality. As one of the newly appreciated post-proton therapy phenomena, RICE lesions have been characterized as small self-limited lesions located at the distal end of the proton beam, with preferential distribution in the periventricular space. Postulated mechanisms for this spatial predilection included higher RBE due to higher LET at the beam end of …

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