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Review Article

Systematic review of MRI alterations in the brain following proton and photon radiation therapy: Towards a uniform European Particle Therapy Network (EPTN) definition

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Highlights

- Systematic review of brain MRI alterations after photon and proton therapy.
- Large heterogeneity in terminology and definitions across included studies.
- Heterogeneity limits conclusions on MRI alterations and role of particle therapy.
- Clinical need for a standardized framework for MRI alterations after radiotherapy.

Abstract

Magnetic resonance imaging (MRI) often demonstrates alterations following cranial radiotherapy (RT), which may result in clinical symptoms and diagnostic uncertainty, and thus potentially impact treatment decisions. The potential differences in MRI alterations after proton and photon RT, has raised concerns regarding the relative biological effectiveness of proton therapy. To provide an overview of MRI alterations in the brain post-RT and to explore differences between photon and proton RT, a systematic review adhering to the PRISMA guidelines was conducted, focusing on the assessment methods and definitions across studies. A systematic search of three electronic databases was performed using the concepts 'normo-fractionated radiotherapy ', 'MRI alterations' and 'brain, skull base or head and neck tumours in adult and paediatric populations'. Data extraction and quality assessment was performed on articles meeting the predefined criteria by two independent reviewers. Out of 5887 screened studies, 94 met the inclusion criteria. These studies were categorized based on confinement of the MRI alterations to temporal lobe, brainstem, or across the entire brain. Additional subclassification was performed based on MRI sequences evaluated or by the nature of the alterations, with pseudoprogression generally reserved for glioma patients. While many papers exist on MRI alterations in the brain after RT, this review highlights significant inconsistencies in the terminology and definitions, limiting the comparability of findings across studies. Our results highlight the need for and facilitate the development of a standardized framework for describing MRI alterations after RT.

Introduction

Radiotherapy (RT) is a cornerstone in the management of primary brain, skull base and head and neck tumours. However, the unavoidable exposure of healthy brain tissue to radiation can result in radiation-induced toxicities including new abnormalities visualized on post-treatment cranial magnetic resonance imaging (MRI). Although these MRI alterations are in many cases not accompanied by symptoms, they can still pose a significant challenge in interpreting post-treatment MRI scans. Differentiating between tumour recurrence, malignant transformation or progression and radiation-induced MRI alterations can be difficult, as the two entities may appear similar. In more severe cases, MRI alterations may progress and be accompanied by neurological symptoms, significantly impacting patients' quality of life, with some symptoms being irreversible [1].

In recent years, the use of proton therapy (PT) for treatment of primary brain and skull base tumours has increased, driven by its growing availability and physical advantages over photon-based radiation therapy (XRT) [2]. The unique depth-dose distribution of PT, the Bragg Peak, allows for better sparing of healthy brain tissue. In PT planning, currently a constant relative biological effectiveness (RBE) of 1.1 is used by all European PT centres, as recommended by Paganetti et al. [3,4]. This RBE value is applied to convert absorbed dose to an RBE weighted dose, accounting for the fact that PT is biologically more effective than XRT. The wide adoption of PT has prompted an increase in investigations on the incidence of radiation-induced toxicities, including MRI alterations after PT. This has raised concerns about the potential correlation

between uncertainties in RBE, and the potential rise in occurrence of MRI alterations following PT.

Past collaborative efforts within the European Particle Therapy Network (EPTN) [[5], [6], [7]], include consensus recommendations on patient follow-up after RT for brain and skull tumours [[5], [6], [7]]. While these recommendations briefly addressed radiological outcome assessment and imaging changes after RT, they did not provide a comprehensive definition of MRI alterations [5]. This review, as part of the ongoing work of the EPTN group, aims to provide a basis to further update and clarify these recommendations on patient follow-up, focussing on MRI alterations observed in the brain on conventional MRI following RT. We excluded more advanced modalities such as MR spectroscopy and positron emission tomography (PET), as MRI remains the primary imaging tool for the follow-up of patients with brain and skull base tumours. The aim of this review is to identify studies on MRI alterations after treatment with RT using conventional fractionation in adult and paediatric patients with primary brain, skull base and head and neck tumours, providing a comprehensive overview of the current evidence, focusing on the assessment methods, definitions, incidence, temporal dynamics and risk factors for the different types of MRI alterations. Additionally, potential differences in MRI alterations across RT treatment modalities, including XRT and PT will be explored. The distinct biological effects of these modalities may lead to variations in the incidence, characteristics, and risk factors of MRI alterations observed in the studies, influenced by the treatment modality applied. Therefore, in this systematic review we aim to provide an extensive overview of the available evidence regarding various MRI alterations in the brain following RT, by consolidating and analysing the definitions, incidence, risk factors, and assessment methods presented in the available studies.

Section snippets

Materials and methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024538901). …

Results

A total of 5887 studies were screened and assessed for eligibility, of which 94 studies were included in this review (Fig. 1: Prisma flowchart). The majority of studies were retrospective

(85/94) and single centre studies (77/94). Most studies were performed in patients treated with XRT (51/94), followed by PT (28/94) and CIRT (3/94). Thirteen studies included both patients treated with XRT and PT. With respect to cohort size, 20 studies included 50 or fewer patients, 18 studies included …

Discussion

This systematic review provides a comprehensive overview of the current evidence on MRI alterations following RT. We identified 94 studies with clear definitions of MRI alterations and categorized them into several types: temporal lobe and brainstem alterations, pseudoprogression, contrast-enhancement only, combined contrast-enhancement and T2/FLAIR, T2 and vascular alterations.

In the 37 studies on MRI alterations after RT for gliomas, PsP was the most commonly reported, while for PT patients …

Conclusion

In conclusion, despite extensive research on MRI alterations after XRT and PT, this review reveals a significant lack of consistency in the terminology and definitions used to describe these alterations. This inconsistency complicates our ability to draw meaningful conclusions regarding incidence, risk factors and clinical implications of MRI alterations, and makes it difficult to compare findings across studies, patient populations, and treatment modalities. Our findings underscore the need …

CRediT authorship contribution statement

Lieselotte Lauwens: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization. **Marvin F. Ribeiro:** Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Catharina M.L. Zegers:** Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Morton Høyer:** Writing – original draft, Supervision, Methodology, …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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