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Development of Ensemble RBE Models for Proton Therapy: A Meta-Synthesis Approach for Evaluating Dose in Critical Organs

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2025 and was last updated on 17 April 2025.

INTRODUCTION

Review question / Objective To explore how different variable RBE models have been used in the literature to estimate biologically weighted doses in proton therapy. This study aims to construct two ensemble RBE (eRBE) models—eRBE-B and eRBE-SC—using a meta-synthesis approach, integrating case numbers and quality scores across relevant studies.
(Population): Patients with head and neck cancer receiving proton therapy, with a focus on dose assessment to the brainstem and spinal cord.
(Intervention): Dose modeling using variable RBE models (Carabe, Wedenberg, McNamara) and meta-synthesis–based ensemble RBE models (eRBE-B and eRBE-SC).
(Comparator): Fixed RBE value of 1.1, which is commonly used in clinical proton therapy.
(Outcomes): Differences in RBE-weighted dose distributions (D_mean, D_max, DVHs) and model-derived stability across critical structures..

Rationale Proton therapy has emerged as a key technique in radiation oncology due to its ability to reduce damage to adjacent healthy tissues while maintaining effective tumor control. However, uncertainties remain in relative biological effectiveness (RBE) calculations, particularly in critical organs at risk (OARs) such as the brainstem and spinal cord. Traditional approaches use a constant RBE value (typically 1.1), which oversimplifies biological dose estimations and neglects important variables such as LET and tissue-specific radiosensitivity. This study aims to construct ensemble RBE (eRBE) models using a meta-synthesis (MS) approach to improve biological dose precision and address variability among existing RBE models. Unlike conventional meta-analyses, this approach aggregates model usage patterns, study quality, and case data, offering an exploratory tool to mitigate modeling biases and support future clinical validation efforts.

Condition being studied This review focuses on dose modeling in head and neck cancers,

specifically the brainstem and spinal cord, which are critical organs commonly exposed in proton therapy. The variability in RBE estimations in these regions may lead to under- or over-estimations of biological doses, potentially impacting treatment outcomes and increasing risk of complications such as neurological dysfunction.

METHODS

Search strategy Databases searched: Web of Science, PubMed, and Scopus.
Example search terms for brainstem-related studies:
("Brainstem" OR "Medulla oblongata" OR "Pons" OR "Midbrain" OR "Mesencephalon") AND
("PT" OR "proton therapy" OR "proton therapies" OR "proton beam therapy" OR "proton beam radiation therapy") AND
("RBE" OR "relative biological effectiveness") AND
("variable RBE" OR "variable relative biological effectiveness" OR "RBE model" OR "RBE models").
Only peer-reviewed studies that incorporated fixed (RBE = 1.1) and variable RBE models in evaluating absorbed dose to the brainstem and spinal cord in cancer patients were included.

Participant or population Patients with head and neck cancer receiving proton therapy, where dose to the brainstem and spinal cord was assessed using both fixed and variable RBE models.

Intervention The intervention includes biological dose modeling using variable RBE models (Carabe, Wedenberg, McNamara), as well as newly constructed ensemble RBE (eRBE-B and eRBE-SC) models through a meta-synthesis approach.

Comparator The fixed RBE value of 1.1 serves as the baseline comparator. Dose estimates generated from the variable RBE models and ensemble models are compared to the fixed RBE estimates.

Study designs to be included Quasi-experimental studies, computational modeling studies, or any publication evaluating biological dose estimation using variable RBE models.

Eligibility criteria Inclusion criteria:
1. Studies involving human or phantom data with proton therapy.
2. Dose assessments focused on brainstem or spinal cord.
3. Must include both fixed RBE (1.1) and at least one variable RBE model.
Exclusion criteria:
1. Studies lacking explicit dose modeling.
2. Reviews, commentaries, or editorials.
3. Studies without sufficient quality information or case data for weighting.

Information sources Web of Science, PubMed, Scopus.

Main outcome(s) The primary outcome is the difference in RBE-weighted dose estimations to the brainstem and spinal cord among different RBE models. Measures include mean dose (D_mean), maximum dose (D_max), and comparisons through dose–volume histograms (DVHs).

Quality assessment / Risk of bias analysis Study quality was assessed using the Joanna Briggs Institute (JBI) checklist for quasi-experimental studies, scoring each included study on 9 criteria.

Strategy of data synthesis Instead of statistical meta-analysis, a meta-synthesis approach was used. Data on model usage frequency, study quality scores, and case numbers were extracted. These values were normalized and weighted to generate two ensemble RBE models: eRBE-B (brainstem) and eRBE-SC (spinal cord).

Subgroup analysis Subgroup synthesis was conducted by anatomical site:
1. eRBE-B: studies modeling the brainstem
2. eRBE-SC: studies modeling the spinal cord
Weights and dose estimates were computed separately for each group.

Sensitivity analysis Sensitivity was indirectly assessed by comparing dose outcomes across five variable models (Carabe, Wedenberg, McNamara, eRBE-B, eRBE-SC) and examining consistency in DVHs and α/β sensitivity (e.g., α/β = 2 for brainstem, 10 for CTV).

Country(ies) involved Republic of China (Taiwan). Taiwan.

Keywords Meta-synthesis (MS), Relative biological effectiveness (RBE), Biological dosage, Head and neck cancer, Model integration.

Contributions of each author
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