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Limitations of EQD2 Accumulation: Why BED Summation is Essential for Accurate Toxicity Evaluation

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ABSTRACT

Purpose: To determine the most radiobiologically consistent method for accumulating dose from differing treatment schedules for both targets and organs-at-risk in reirradiation scenarios.

Methods: We analyzed paired dose distributions from serial plans (66 and 20 Gy) with mixed fractionation schedules (2- and 5-Gy/fraction, respectively) for a central nervous system cancer patient reirradiation. We evaluated accumulated doses in terms of equivalent dose in 2-Gy fractions (EQD2) and biological effective dose (BED). Biological conversion utilized a fixed α/β-ratio of 10 Gy for the planning target volume (PTV) and 2 Gy for the spinal cord, assuming α=0.1 Gy^{-1} under the linear-quadratic model. We identified the isoeffective 2-Gy/fraction schedule for the 5-Gy/fraction plan. We used the accumulated EQD2 and total number of fractions to derive local dose-per-fraction. The objective biological effect endpoint was negative natural log surviving fraction (E=−lnSF) for the mean PTV dose and the maximum cord dose (for conservative toxicity risk evaluation). Ground truth was the sum of −lnSF between the two plans, with an acceptance criterion of <3% absolute error.

Results: The 5-Gy/fraction plan of 20 Gy was equivalent to a 2-Gy/fraction plan of 25 Gy. For the 2-Gy/fraction and 5-Gy/fraction plans, respectively, the mean PTV dose was 67.1 and 23.7 Gy and the max cord dose was 42.4 and 18.4 Gy. Dose summation using EQD2 was accurate for PTV (1.4% error) but failed for the cord (14.1% error). This failure arises because EQD2 conversion rigidly applies a reference (2-Gy/fraction) plan-level assumption that neglects the local low dose-per-fraction reality in the organs-at-risk. Only BED summation met the acceptance criterion for both PTV and cord (0% error).

Conclusions: BED summation provides the most mathematically robust framework for composite planning. While direct EQD2 summation is clinically common, it requires caution in organs-at-risk where the reference fraction size differs significantly from the local dose-per-fraction.

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INTRODUCTION

Reirradiation poses complex clinical scenarios, and these cases are on the rise with patients surviving longer. Of critical importance is toxicity risk evaluation for dose limiting organs at risk.

Currently, the Reirradiation Collaborative Group (ReCOG) consensus recommends accumulation of "equieffective" doses.[1] Among the most widely used isoeffective dose models is the equivalent dose in 2-Gy fractions (EQD2) formulation

$$EQD2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

which is linked to the biological effective dose (BED) model $BED = D\left(1 + \frac{D/n}{\alpha/\beta}\right) = nd\left(1 + \frac{d}{\alpha/\beta}\right)$ derived from the linear-quadratic (LQ) model for cell survival $SF = \exp(-\alpha nd - \beta nd^2)$ where the d is the uniform absorbed dose per fraction, n is the total number of fractions, and α and β are radiosensitivity fitting parameters.

This study aims to evaluate current limitations and identify an optimal radiobiological method for dose accumulation across differing fractionation schedules in reirradiation, for both target volumes and organs at risk.

METHODS AND MATERIALS

- Analyzed **paired dose distributions from serial plans of a CNS reirradiation case** (Figure 1, patient data rather than simplified phantoms):
  - H&N IMRT: 66 Gy (2 Gy/fraction)
  - Then 11.3 months between plans
  - Brain SRS: 20 Gy (5 Gy/fraction)
- Evaluated accumulated dose using:
  - Equivalent dose in 2-Gy fractions (EQD2)
  - Biological effective dose (BED)
- Applied linear-quadratic model for biological conversion using parameters from Table 1

Table 1. Radiobiology parameters (LQ Model).

	α (Gy^{-1})	α/β (Gy)	β (Gy^{-2})
PTV	0.1	10	0.01
Spinal Cord	0.1	2	0.05

- Identified isoeffective 2 Gy/fraction schedule corresponding to the 5 Gy/fraction plan
- Derived local dose per fraction from:
  - Accumulated EQD2
  - Total number of fractions
- Defined **biological effect endpoint** (first-principles radiobiology applied to complex real-world data):
  - $E = -\ln SF = \alpha \cdot BED = \alpha nd + \beta nd^2$
    - SF is the surviving fraction
    - d is the absorbed dose per fraction
    - n is the number of fractions
  - Evaluated at:
    - **Mean PTV dose**
    - **Maximum spinal cord dose** (for conservative toxicity estimate)
- Established **ground truth** as:

$$\sum_i -\ln SF_i = E_{IMRT} + E_{SRS}$$

- **Acceptance criterion**: <3% absolute error

RESULTS

According to the corresponding SF from the parameterized LQ model, the 5-Gy/fraction brain SRS plan of 20 Gy was equivalent to a 2-Gy/fraction plan of 25 Gy. The different characteristics and endpoints are summarized in Table 2 for each plan (Figure 1).

Table 2. Plan doses (11.3 month interval) and biological endpoints.

		H&N IMRT	Brain SRS	Sum
Prescribed Dose		66 Gy	20 Gy	-
Delivered Fractions		33	4	-
Dose per Fraction		2-Gy/fx	5-Gy/fx	-
Equivalent 2-Gy/fx Prescribed Dose		66 Gy	25 Gy	**91 Gy**
Physical Dose	Spinal Cord	42.4 Gy	18.4 Gy	**60.8 Gy**
	PTV	67.1 Gy	23.7 Gy	**90.8 Gy**
BED	Spinal Cord	69.6 Gy	61.0 Gy	**130.6 Gy**
	PTV	80.7 Gy	37.7 Gy	**118.4 Gy**
EQD2	Spinal Cord	34.8 Gy	30.5 Gy	**65.3 Gy**
	PTV	67.2 Gy	31.5 Gy	**98.7 Gy**

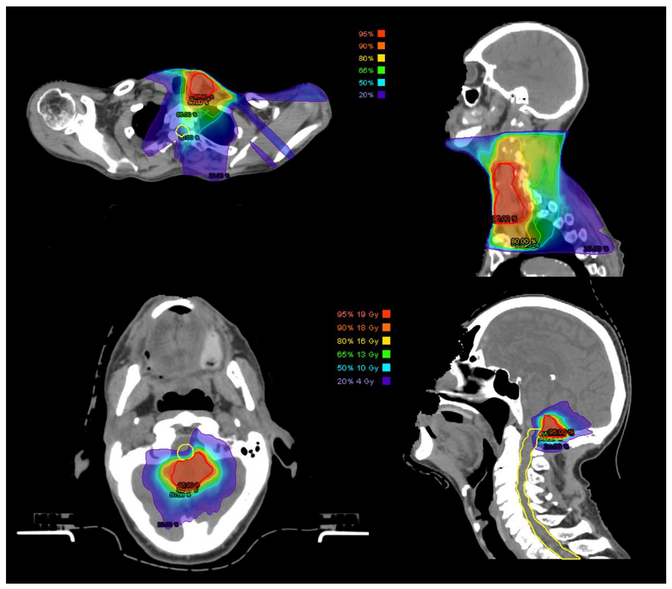

Figure 1. Dose distributions for a head and neck IMRT plan (top) delivered in 66 Gy over 33 fractions (2-Gy/fx) and—11.3 months later—a brain SRS plan (bottom) delivered in 20 Gy over 4 fractions (5-Gy/fx).

Relative to the <3% absolute error acceptance criterion, dose summation using EQD2 was accurate for PTV (1.4% error) but failed for the Spinal Cord (-14.1% error) per Figure 2. Only BED summation met the acceptance criterion for both PTV and Spinal Cord (0% error).

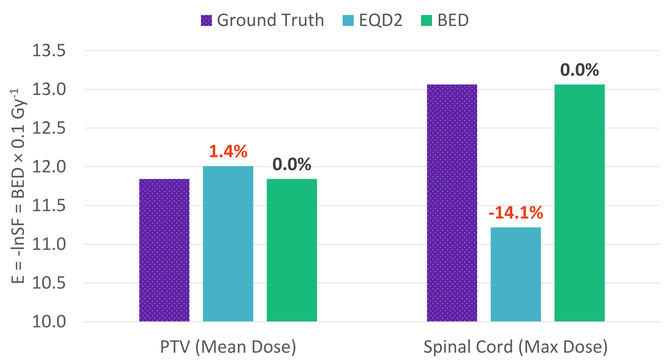

Figure 2. Biological effect (E) of EQD2 ($EQD2_{IMRT}$ + $EQD2_{SRS}$) and BED (BED_{IMRT} + BED_{SRS}) dose summations and absolute percent errors from the ground truth.

DISCUSSION

The validity of the accumulation is derived from the multiplicative nature of independent survival probabilities, which mathematically necessitates the additivity of BED: $SF_{total} = \prod_i SF_i$
$\Rightarrow -\ln SF_{total} = \sum_i \ln SF_i \Rightarrow BED_{total} = \sum_i BED_i$
In contrast, the EQD2 metric utilizes a fixed reference fraction size ($d_{ref} = 2\ Gy$) that mathematically decouples the EQDX metric from local cell kill when the local fraction size differs from the reference:

$$EQDX = \frac{BED}{1 + \frac{d_{ref}}{\alpha/\beta}}$$

By evaluating errors against the foundational SF equations rather than abstracted surrogate metrics, we ensure the reported discrepancies reflect true biological divergences.

These findings are of immediate interest to clinical physicists and planners managing reirradiation cases, as they highlight limitations in standard clinical workflows. This study advocates for improved precision in effective dose assessment to build confidence when evaluating accumulated radiation plans from differing treatment schedules, which is increasingly common in clinical practice with reirradiation and composite radiotherapy planning

This is an aspect to be considered for the advancement of enhanced biological models as recommended by ReCOG.[1] This may include approaches like the equivalent physical dose concept or focus on BED-specific models which consider the limitations of EQD2 accumulation.

CONCLUSIONS

This work identifies and quantifies a potential gap in the rising practice of CNS reirradiation, where accurate estimation of cumulative spinal cord doses is crucial for delivering safe and effective treatment plans.

We highlight limitations of the commonly used EQD2 approaches by explaining the root cause: EQD2 calculations rely on the premise that the OAR receives the full 2-Gy fraction size meant for the tumor, which effectively overlooks the smaller doses per fraction it actually absorbs. By mathematically isolating these mechanisms, we are helping to raise awareness in the medical physics community about existing limitations and avenues for more consistent biological modeling.

BED summation provides the most mathematically robust framework for composite planning. While direct EQD2 summation is clinically common, it requires caution in organs-at-risk where the reference fraction size differs significantly from the local dose-per-fraction.

REFERENCES

1. Paradis KC, Appelt AL, Bentzen SM, et al. Reirradiation Collaborative Group (ReCOG) consensus on standards for dose evaluation and reporting in patients with multiple courses of radiation therapy: an AAPM/ACRO/ASTRO/CARO/COMP/CADRA/CPQR/ESTRO/NRG-endorsed consensus statement. *The Lancet Oncology*. 2026;27(2):e101-e110. doi:10.1016/S1470-2045(25)00562-5