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Can Empirical RBE Models Predict Variations in Intrinsic Radiosensitivity?

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ABSTRACT

Purpose: To assess the accuracy of empirical relative biological effectiveness (RBE) models in predicting variations in intrinsic radiosensitivity using a comprehensive dataset of clonogenic cell survival.
Methods: A dataset composed of 46 pancreatic cancer cell lines, irradiated with a constant dose-averaged linear energy transfer (LET) of 3.85 keV/µm, was used to extract radiosensitivity metrics, including $D_{10\%}$, $D_{50\%}$, mean inactivation dose and survival fraction at 2 Gy with their corresponding RBEs. Eleven RBE models were retrained on this dataset using the leave-one-out cross-validation method, with minimizing the root mean squared error (RMSE) for either α and β values, or RBE at a specific endpoint. The goodness-of-fit for each model before and after retraining was reported in terms of the RMSE, reduced chi-squared statistic (χ^2_{red}), and Bayesian information criterion (BIC). Additionally, the dataset was categorized into four groups based on cell line radiosensitivity to assess at which level of radiosensitivity the models perform more accurately.
Results: Most models showed similar RMSE and χ^2_{red} values with a similar trend for all endpoints. However, poor RBE predictions were observed for three models, likely attributed to how these models were first derived and their functional expressions, which limit their use to conditions (LET and α and β values) outside the conditions they were derived. Although models with more complex functional forms outperformed the others, those with simpler expressions achieved the best BIC scores. Model retraining improved prediction accuracy, with some models showing substantial improvements. Overall, the models exhibited better accuracy for radioresistant cell lines.
Conclusions: Our findings suggest that it is best to retrain RBE models to a specific dataset that closely represents the range of LET, and α and β values in which they will be utilized. However, inaccuracies in RBE predictions are still present, highlighting incorporating intrinsic biological/genomic characteristics into future RBE models.

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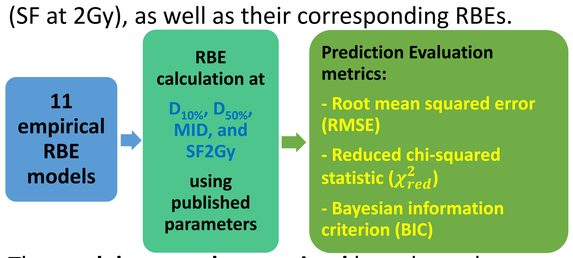
INTRODUCTION

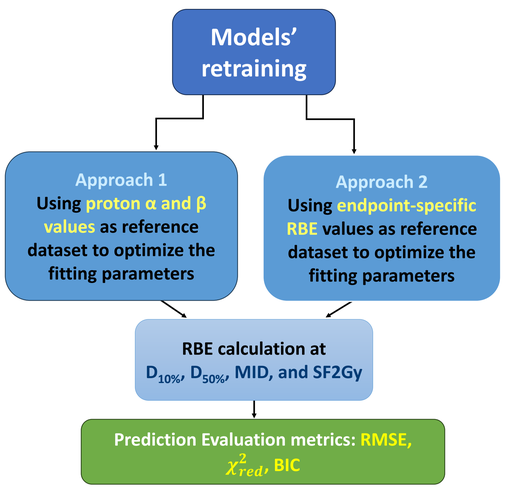
The constant relative biological effectiveness (**RBE**) value of **1.1 is used clinically** for proton radiotherapy (1), even though **it overlooks the influence of biological and physical factors** on RBE variation. It has been demonstrated that the RBE depends significantly on the genomic characteristics of cancer cells due to differences in the DNA damage response to protons (2). **Most current empirical RBE models** incorporate physical and biological factors such as **LET and α and β values** extracted by the linear-quadratic (LQ) model to estimate RBE using a general formalism.
Although these models are based on a common mathematical framework, differences in the **datasets used to develop these models** were generated by different research groups **under varying experimental conditions**, making it difficult to isolate and accurately quantify the contribution of intrinsic radiosensitivity to RBE. To address this limitation, **we evaluated current RBE models using our comprehensive RBE dataset**, which was obtained under **highly consistent experimental conditions** (3). This approach enables us to assess the accuracy of existing models in a setting where intrinsic radiosensitivity is the primary variable.

METHODS AND MATERIALS

In this study, we utilized a **clonogenic cell survival dataset of 46 pancreatic cancer cell lines** acquired under consistent conditions and a **constant proton LET** of 3.85 keV/µm (3). The database contains radiosensitivity metrics like $D_{10\%}$, $D_{50\%}$, mean inactivation dose (MID) and survival fraction at 2 Gy (SF at 2Gy), as well as their corresponding RBEs.



The **models were also retrained** based on a leave-one-out cross-validation (**LOOCV**) method and the RMSE served as a loss function.



Moreover, the **cell lines were categorized** as Very Radiosensitive, Intermediate-Radiosensitive, Intermediate-Radioresistant, and Very Radioresistant **to assess how models' performance varies among different radiosensitivity groups**.

RESULTS

The models' accuracy before retraining with the dataset was tested at four different endpoints of RBE at $D_{10\%}$, $D_{50\%}$, MID and SF at 2Gy. Some models, such as **Wedenberg, McNamara, Rorvik and Flint**, demonstrated **better performance** in terms of RMSE and reduced chi-squared statistic (χ^2_{red}), whereas Chen, Wilkens and Jones models yielded poor RBE predictions (Figure 1.A&B). However, some models outperformed others in terms of the BIC, which reflects both model accuracy and complexity (Figure 1.C). The models were also **retrained with two different approaches**, either **using proton α and β datasets** (only RBE at $D_{10\%}$ values are shown in Figure 2.A-C) or **RBE values at a specific endpoint** (Figure 3.A-C). **Both approaches improved the prediction accuracy of the models** across all evaluated endpoints. However, the latter approach resulted in more accurate predictions at the cost of requiring multiple endpoint-specific fitting parameters, which may limit its generalizability. Finally, the models' prediction accuracy was assessed at various radiosensitivity levels: Very radiosensitive, Intermediate-radiosensitive, Intermediate-radioresistant, and Very radioresistant. Overall, **the models predicted the RBEs more accurately for the very radioresistant cell lines** at most of the endpoints, as shown in Figure 4. In conclusion, the models exhibited a wide range of discrepancies relative to experimental values, mainly arising from differences in their fitting assumptions and databases in which they were originally derived.

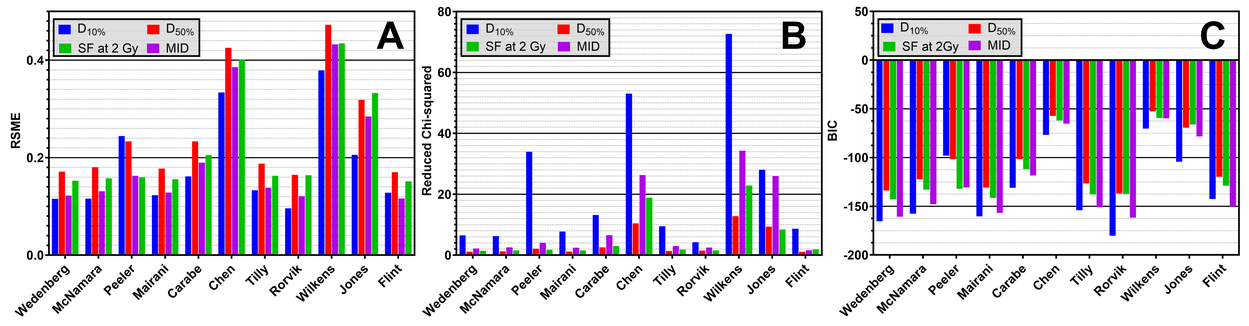


Figure 1. Statistical metrics at various endpoints **before retraining**. (A) RMSE, (B) χ^2_{red} and (C) BIC.

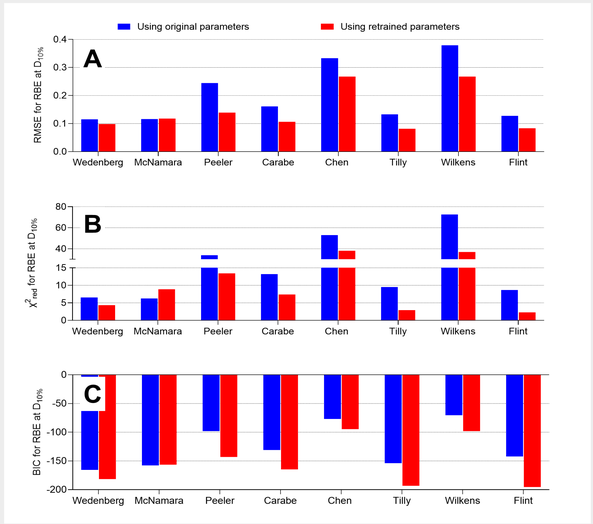


Figure 2. Statistical metrics for each RBE model using both original parameters and model parameters estimated from **retraining with α and β values**. (A) RMSE, (B) χ^2_{red} and (C) BIC for RBE at $D_{10\%}$.

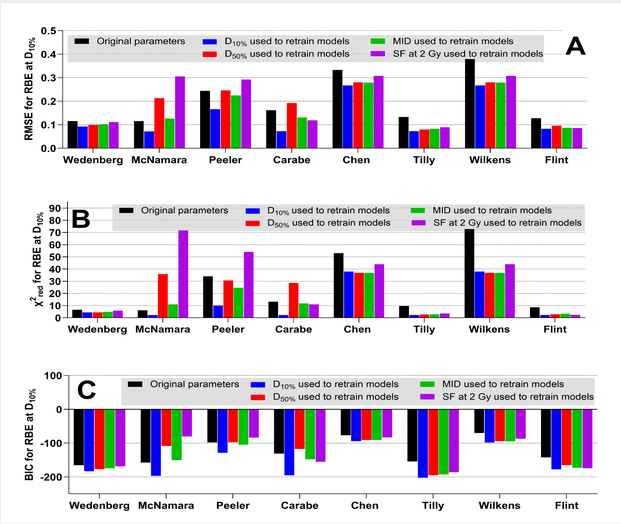


Figure 3. Statistical metrics for each RBE model using both original parameters and model parameters estimated from **retraining with different endpoint-specific RBE values**. (A) RMSE, (B) χ^2_{red} and (C) BIC for RBE at $D_{10\%}$.

CONCLUSIONS

We assessed how accurately the available proton RBE models capture the **variation driven solely by intrinsic radiosensitivity**. This approach was implemented using our robust radiosensitivity database acquired at a constant LET. **The models' accuracy** in RBE prediction **varied significantly** compared to the experimental values, depending on the given endpoints and the metrics used to evaluate them. The findings reflect **differences in assumptions and databases** used for the models' fitting process. Although the models' performance improved in most cases after retraining using our robust dataset, significant variability remained across different radiosensitivity groups. It highlights the importance of **incorporating determinative biological features beyond standard LQ metrics** into future proton RBE models.

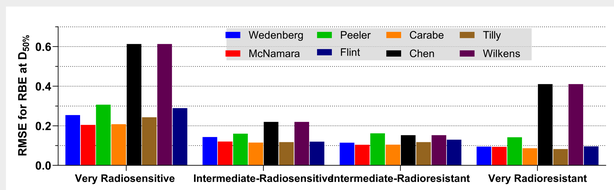


Figure 4. RMSE values of each model at **different levels of radiosensitivity** for RBE at $D_{50\%}$.

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