A fully predictive approach to compute NTCP curves for radiation-induced myelopathy in rats exposed to clinically-relevant ions

2026 JOINT AAPM | COMP MEETING
JULY 19–22 | VANCOUVER, BC

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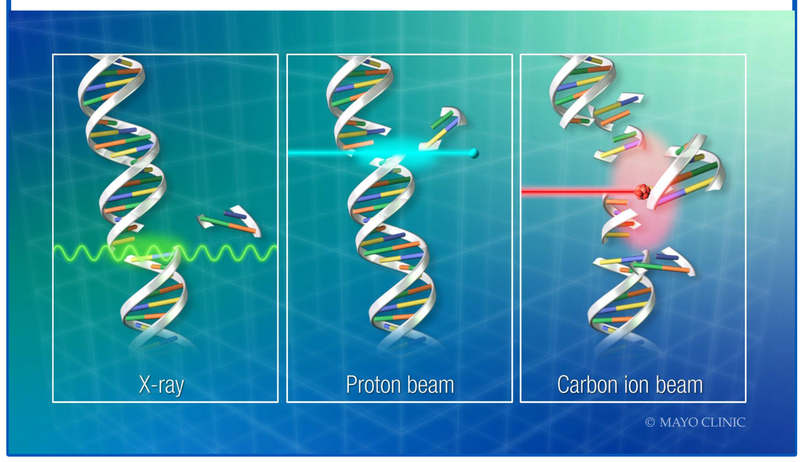
BACKGROUND

- **Carbon ion radiotherapy** is an advanced form of radiation therapy that offers physical and **biological advantages**, especially **against radioresistant and hypoxic tumors**
- There are < 20 carbon ion therapy centers currently in operation around the world (Japan, Germany, Italy, China, Austria, South Korea, Taiwan)
- **Mayo Clinic Florida** is installing the **first carbon ion radiotherapy center in the Americas**
- Compared to X-rays of conventional therapy, **carbon ions have greater relative biological effectiveness (RBE)** in inducing lethal damage (up to 20 at low doses)
- Due to limitations of current models, we developed the Mayo Clinic Florida microdosimetric kinetic model (**MCF MKM**) and **extensively validated** its ***in vitro*** predictions for 30+ cell lines



THE MODELING FRAMEWORK

THE NTCP MODEL

Based on the critical volume model (Niemierko and Goitein, 1993)

$$NTCP = 1 - \left\{1 - \left[1 - exp\left(-\alpha D - \frac{\beta D^2}{n}\right)\right]^{\frac{N_{cells}}{N_{FSUs}}}\right\}^{N_{FSUs}}$$

2 radiation-independent parameters
N_{FSUs} → total number of **exposed FSUs**
N_{cells} → total number of **exposed cells**

2 radiation-dependent parameters
α → linear term of cell survival
β → quadratic term of cell survival

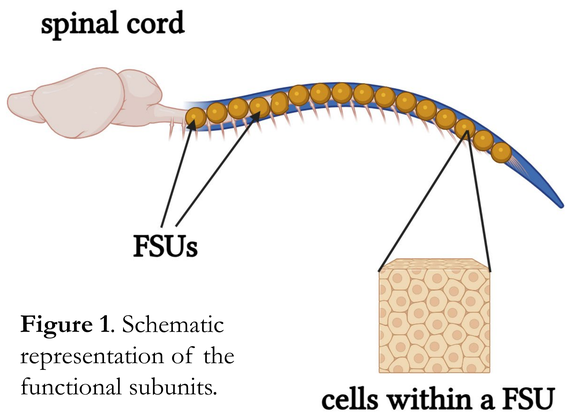


Figure 1. Schematic representation of the functional subunits.

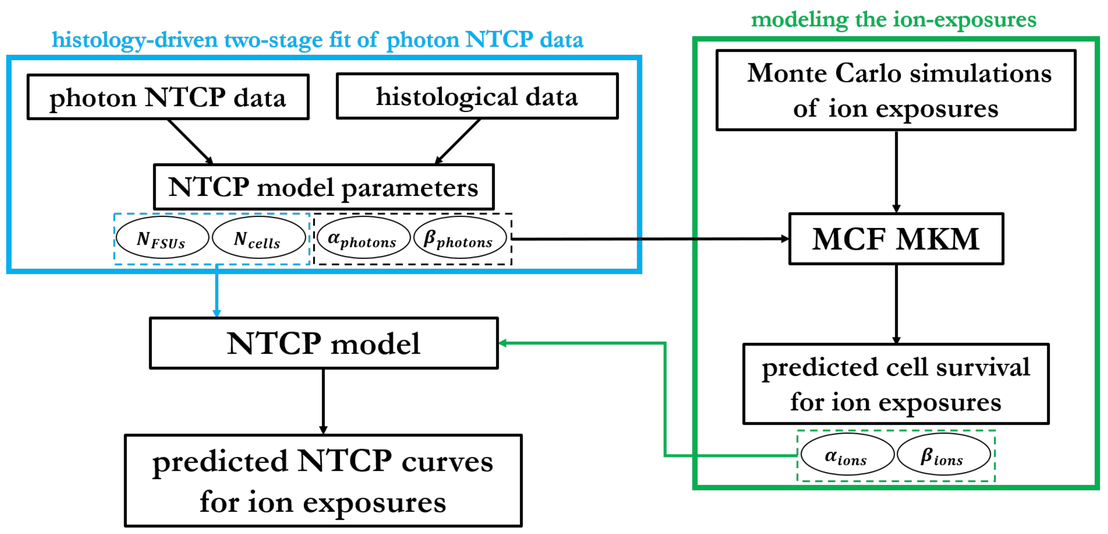


Figure 2. Schematic representation of the methodology used in this study.

APPROACH:

- Derive radiation-independent parameters (N_{FSUs} and N_{cells}) and photon cell survival ($\alpha_{photons}$ and $\beta_{photons}$) by fitting NTCP photon data in conjunction with published histological data (segment-dependent white matter cross-section, cell density) for two hypothetical targets: glial and endothelial cells
- Knowing $\alpha_{photons}$ and $\beta_{photons}$, use MCF MKM (microdosimetry-based RBE model) to estimate α_{ions} and β_{ions} for the ion exposures
- Knowing α_{ions} and β_{ions}, predict the NTCP curves for the ion exposures

NB: NO ION DATA USED AS CALIBRATION AT ANY STAGE

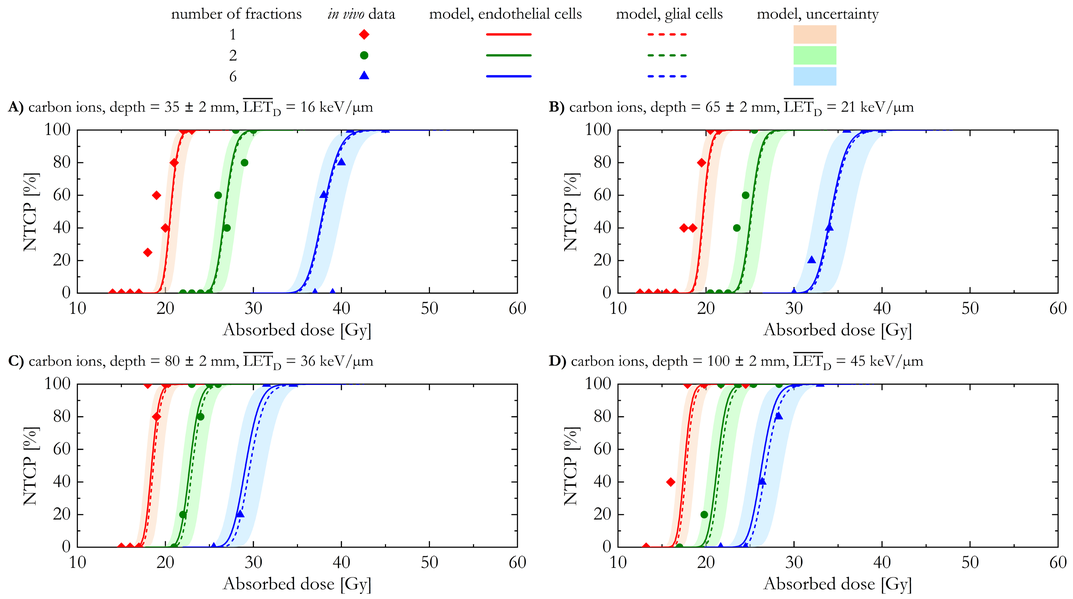


Figure 3. NTCP curves of rat spinal cord myelopathy for fractionated exposures along the carbon ion SOBP. The model predictions (lines) are compared to corresponding experimental data (symbols).

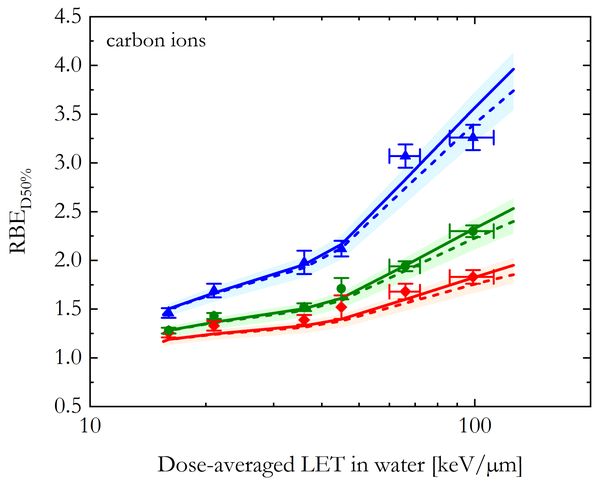


Figure 4. The RBE for 50% NTCP as a function of the dose-averaged LET for fractionated exposures at different depths along the carbon ion SOBPs.

CONCLUSIONS

Using only photon NTCP data and histological information, the framework predicted rat spinal cord myelopathy after proton, helium, carbon and oxygen irradiation without ion-specific calibration, reproducing the observed dependence on fractionation, ion species, and position along the SOBPs.