Estimating Cell Survival in Ac-225-PSMA Radionuclide Therapy Using PBPK Modeling, Monte Carlo Simulation, and the Two-Lesion Kinetic Model Considering Time-Dependent Dose Rate

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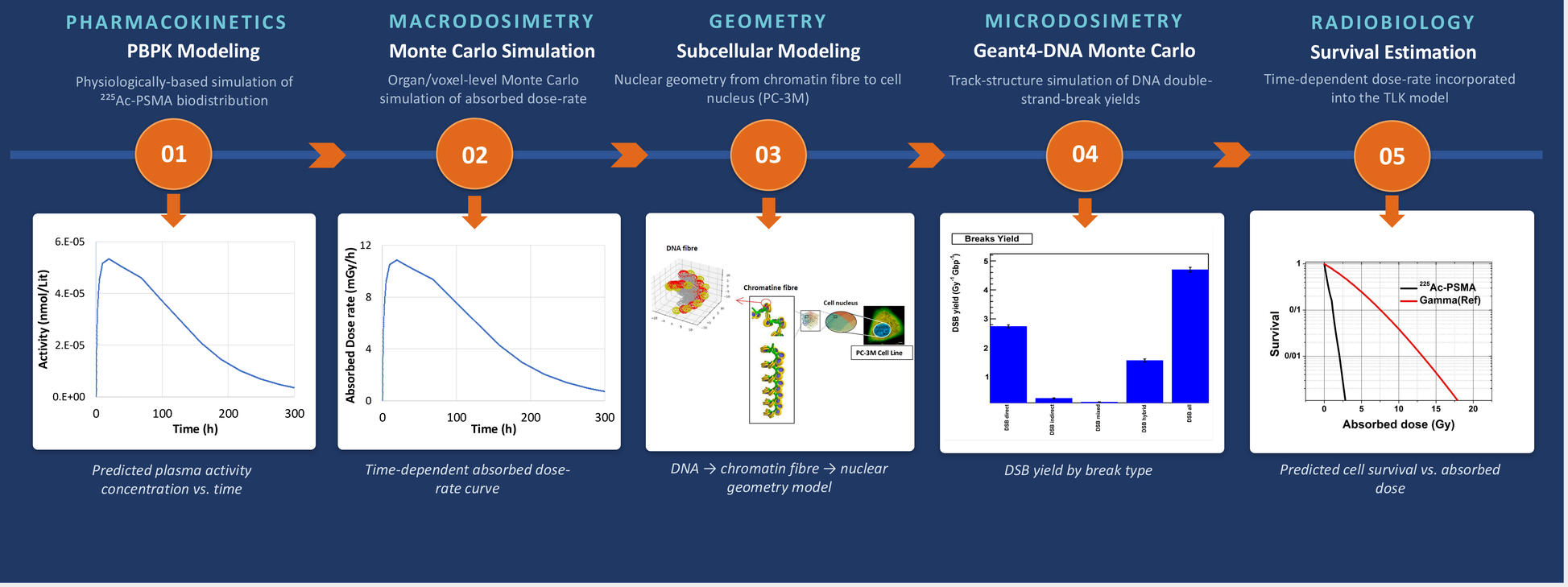
Aim

This study aims to estimate prostate cancer cell survival following Ac-225-PSMA targeted radionuclide therapy by integrating physiologically based pharmacokinetic (PBPK) modeling, Monte Carlo-based macroscopic dosimetry using GATE, subsequent microscopic dosimetry using GEANT4-DNA, and the two-lesion kinetic (TLK) radiobiological model, while explicitly accounting for temporal variations in absorbed dose rate.

Methodology

Multiscale Dosimetry & Radiobiological Modeling Pipeline



Predicted plasma activity concentration vs. time | *Time-dependent absorbed dose-rate curve* | *DNA → chromatin fibre → nuclear geometry model* | *DSB yield by break type* | *Predicted cell survival vs. absorbed dose*

METHODS AND MATERIALS

The spatiotemporal distribution and time–activity curve of Ac-225-PSMA in prostate cancer tumors were first simulated using a PBPK model. Tumor absorbed dose was subsequently calculated using Monte Carlo simulations in GATE based on the dose point kernel method. DNA damage induction, quantified as double-strand breaks (DSBs), was then simulated at the cellular level for PC3 cells using Geant4-DNA. DNA damage repair kinetics were modeled using the Belov repair model to derive the Lea-Catcheside (LC) factor, which accounts for continuous dose-rate reduction effect on survival. Finally, cell survival following Ac-225-PSMA irradiation was estimated using the TLK model incorporating the calculated LC values.

RESULTS

PBPK modeling yielded the tumor time-integrated activity curve for Ac-225-PSMA, and subsequent Monte Carlo simulations showed that the absorbed dose delivered to a 2-cm tumor was 15.82 Gy per 1 $\mu mol \cdot m^{-3}$ of injected activity. Geant4-DNA simulations provided DSB yields and repair dynamics, from which LC values were obtained. Using the TLK model, the survival fraction (SF) of PC3 cells following 2 Gy irradiation was estimated to be 0.011 ± 0.005, in close agreement with previously reported experimental values (SF = 0.015 ± 0.005).

DISCUSSION

In this study, we first obtained the time-activity curve of Ac-225-PSMA in tumors using a PBPK model. Subsequently, macroscopic dosimetry simulations were performed in GATE employing the point kernel method to calculate the absorbed dose and dose-rate curve over time. At the cellular level, Monte Carlo simulations were used to spatially model DNA damage induction. By applying the TLK model, which accounts for temporal variations in dose rate, we derived the cell survival curve following Ac-225-PSMA irradiation. The results showed good agreement with experimental data. This work is the first to combine PBPK and TLK models alongside both macroscopic and microscopic Monte Carlo simulations, providing a comprehensive framework capable of accurately predicting cellular response to targeted radionuclide therapy. Therefore, this approach can be considered an important step toward developing a digital twin for optimizing radionuclide treatments.

CONCLUSIONS

These results demonstrate that combining PBPK modeling, Monte Carlo simulations, and the TLK cell survival model, while accounting for time-dependent dose-rate effects provides a robust framework for estimating cellular survival in Ac-225-PSMA radionuclide therapy across varying spatial and temporal activity distributions within tumors.

REFERENCES

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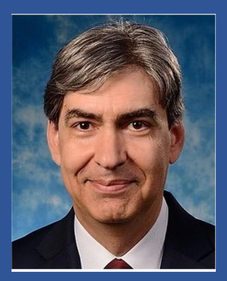

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