Background: Although ionizing radiation induces DNA double-strand break (DSB) in tumor cells which leads to tumor degradation, it also causes the up regulation of PD-L1 expression by cancer cells. PD-L1 on the surface of tumor cells form a complex with PD-1 on the plasma membrane of CTLs that induces exhaustion/inactivation in CTLs. CTL as a major component of the adaptive immune system plays a pivotal role in antitumor immunity. The anti-PD-L1 therapy enables CTLs to remain active and ample experimental evidence has proven that it synergizes with RT. The complex interactions of these treatments call for system approaches to deepen our understanding and to expand our knowledge.

Methods: We developed a mathematical model based on ordinary differential equations to simulate the interactions of radiotherapy and blockade of programmed death-ligand-1 (PD-L1) in hepatocellular carcinoma (HCC). The variables include cancer cells, cytotoxic T lymphocytes (CTLs), programmed death-1 (PD-1), programmed death-ligand-1 (PD-L1), anti-PD-L1, and ionizing radiation. Model is parameterized with imprecise in vivo data of HCC and the effect of parametric uncertainty is assessed by the fuzzy theorem. The global sensitivity analysis is performed to assess model robustness against perturbation in parameters.

Results: In silico predictions are consistent with experimental data. The model simulation shows anti-PD-L1 and radiotherapy have a synergistic effect. In silico assessment of treatments’ efficacy in the fuzzy setting of parameters revealed that anti-PD-L1 therapy, radiotherapy, and combination treatment caused the uncertainty band of tumor cells to lead to lower populations.

 Conclusion: This model as a validated rigorous simulation framework can be used to deepen our understanding of tumor and immune cell interactions and helps clinicians to investigate the efficacy of different time schedules of anti-PD-L1, radiotherapy, and combination therapy. The fuzzy theorem in conjunction with the classical ODE model that is parameterized by imprecise data was used to predict reliable outcomes of treatment efficacy.

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$\frac{dA\_{T}}{dt}=-(k\_{T1}+k\_{el})A\_{T}$ Anti-PD-L1 injection

$\frac{dA\_{1}}{dt}=k\_{T1}A\_{T}-k\_{T2}A\_{1}$ Intercompartment Anti-PD-L1 transfer

 $\frac{dA\_{2}}{dt}=k\_{T2}A\_{1}-k\_{T3}A\_{2}$ Intercompartment Anti-PD-L1 transfer

$\frac{dR\_{1}}{dt}=-k\_{1}R\_{1}$ Radiotherapy dose decay

$\frac{dR\_{2}}{dt}=k\_{1}R\_{1}-k\_{2}R\_{2}$ Radiotherapy dose decay

 $\frac{dR\_{3}}{dt}=k\_{2}R\_{2}-k\_{3}R\_{3}$ Radiotherapy dose decay

$\frac{dU}{dt}=p\_{r}R\_{3}-\frac{U}{T\_{u}}$ DNA double strand break

$\frac{dC}{dt}=a C \left(1- \frac{C}{b} \right)-\frac{c T C}{d+T}-\left(\frac{k R\_{3}}{m+R\_{3}}+p U^{2}\right)C-e C$ Cancer cell dynamics

$\frac{dT}{dt}=(p\_{12}+p\_{2}T)\frac{z}{(x\_{1}+x\_{2}PL.PD)}-\frac{x\_{4}R\_{3} T}{x\_{5}+R\_{3}}-x\_{3}T$ CTL dynamics

$\frac{dPL}{dt}=v\left(wC+hT\right)-\frac{sA\_{2}PL}{u+ A\_{2}}-q PL$ PD-L1 dynamics

$\frac{dPD}{dt}=v\left(1-h\right) T-r PD$ PD-1 dynamics