Original Article

Estimation of electromagnetically controlled ionizing radiation therapy effectiveness based on probabilistic modeling

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Abstract

Background: Various radiobiological models aim to estimate crucial tumor cell (TC)-killing effects for radiotherapy and radiation risk assessment, each with unique applications. This paper presents a specific probabilistic model for predicting tumor control probability (TCP) and introduces a user-friendly standalone simulation app tailored for this purpose.

Methods: A pragmatic probabilistic model is suggested for estimating TCP by incorporating a fractionated treatment approach. Within this model, ionizing radiation induces the formation of killed cells, sublethally damaged cells, and undamaged cells (UDC), the impact of which is contingent upon the radiosensitivity of cells. This triad of cell types can be influenced by radiation during subsequent fractions, providing a nuanced understanding of the treatment dynamics.

Results: A MATLAB app has been developed for a TCP simulator. This simulator employs probabilistic modeling to describe radiation biological effects in a tumor subjected to homogeneous irradiation with a specified dose per fraction in a fractionated treatment. The key input parameters for the simulation include a cell radiosensitivity of 1.2, radiosensitivity of cell sub-lethal damage at 3, TC volume of 1 cm^3, TC density of 0.1×10^7, 30 virtual simulations, and 40 fractional radiation doses. Postsimulation, the resulting TCP is determined to be 86.7%.

Conclusion: The study's simulator is a crucial tool for modeling radiation-induced biological effects in fractionated irradiation of tumors. Its use of probabilistic foundations generates hypotheses and assesses the efficacy of fractionated radiation therapy, holding promise for enhancing the safety and effectiveness of cancer treatment.

Keywords: Cell radiosensitivity, radiobiological models, radiotherapy, tumor control

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INTRODUCTION

The environment is full of natural as well as artificial electromagnetic fields of varying frequencies and strengths. The Earth's magnetic field and the body's own metabolic processes are the two examples of natural sources, whereas external, artificial fields result from the production, transmission, and use of electricity. These electromagnetic field radiations are broadly classified as ionizing and nonionizing radiation. Ionizing emission is

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an example of radiation that has sufficient energy and can detach electrons from the molecule or atom. The particles of the ionizing radiation generally travel with a speed >1% of the light. The example of ionizing radiation is gamma rays, X-rays, and the higher ultraviolet part of the light. Alpha particles, beta particles, and neutrons are the particles of ionizing radiation. These particles are produced as a result of radioactive decay. Nonionizing radiation is a type of radiation that holds sufficient strength to shift the fragment in the smallest part throughout or aim electrons to shake. Very small wavelength waves, radio waves, microwaves, infrared, and visible light are the examples of nonionizing emissions. Uncontrolled nonionizing radiation can also cause some health issues.[1-4] In the scientific community, electromagnetic radiation has been the subject of extensive research, particularly with regard to its effects on living organisms. Many studies reveal that exposure to electromagnetic radiation can have a variety of impacts on human health, including changes to sleep patterns, hormone levels, and immune function.[5-7] In addition, there have been concerns about the potential carcinogenic effects of long-term exposure to extremely low-frequency radiation (WHO), although the evidence for this remains inconclusive.[8-10]

This article comprehensively examines the diverse radiation therapy methods and conducts a thorough review of various radiobiological models pertaining to cancer cell treatment. The development of a user-friendly simulation app utilizing a probabilistic modeling approach is presented, followed by a detailed presentation of results, discussions, and a conclusive summary.

METHODS

Radiation therapy

Radiation therapy is one of the cancer treatment methods among other cancer treatment methods such as chemotherapy, hormone therapy, hyperthermia immunotherapy, stem cell transplant, targeted therapy, and surgery. For radiotherapy treatments, linear accelerators are used that employ collimators or beam-limiting devices. They also have the capability to establish the maximum field size of a beam and contribute to shaping the radiation beam emitted by the machine. In modern radiation systems, multi-leaf collimators (MLCs) are utilized to further shape a beam and localize treatment fields.[11] In radiation therapy, an electromagnetically controlled precise external beam is locally pointed at a specific part of the body. These ionizing radiations have enough energy to kill or shrink the cancer tissue without affecting the normal tissues. The amount of radiation (dose) and time duration are decided by the type of cancer, radio sensitivity of the cell, volume of the cell, and cell density of the affected body part. Photon, electron, and proton particle beams are used in external-beam radiation therapy.

The majority of radiation therapy devices employ photon beams, with X-rays also harnessing photons, although at significantly lower doses. Photon beams are adept at reaching deep-seated malignancies within the body. As they traverse through the body, these beams exhibit minimal radiation dispersion. Notably, after passing through the tumor, these beams persist through the adjacent normal tissue rather than coming to a halt.[12]

Proton beam radiation therapy is also another way to treat cancer. Proton beams exhibit a capacity comparable to photon beams in effectively penetrating deep-seated tumors within the body. Unlike photon beams, however, proton beams continue their trajectory beyond the tumor without dispersing radiation during their passage through the body. Medical experts anticipate that proton beams hold promise in minimizing radiation exposure to healthy tissues. Ongoing clinical studies are underway to compare the efficacy of radiation therapy employing photon beams versus proton beams.[12] While proton beams find application in radiation therapy across various cancer facilities, their widespread adoption is hindered by the constraints posed by costly and substantial equipment.

Electromagnetically controlled electron beam radiation therapy makes the use of intense electron particle beam to treat cancer. High attenuation of electron beams passing through body tissues restricts the use of electron beam radiation therapy as electron beams cannot travel deep into the body. Their application is thus restricted to tumors that are located close to or on the skin's surface.[13]

External-beam radiation therapy manifests in diverse modalities, including three-dimensional (3-D) conformal radiation therapy, intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), tomotherapy, stereotactic radiosurgery, and stereotactic body radiation therapy. All of these aim to provide the tumor with the maximal recommended dose of radiation while preserving the surrounding healthy tissue. Suitable radiation therapy is used to treat cancer cells depending on the type, stage, shape, position, and form (solid or liquid) of cancer. Each type uses a computer to evaluate tumor images and determine the exact dose and course of treatment.

A highly favored variant of external beam radiation therapy is 3D conformal radiation therapy, wherein simulation

serves as the meticulous approach for precisely delineating the treatment area, leveraging computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. Advanced computer software analyzes these images and generates tailored radiation beams that align with the structure of the tumor. Properly shaped beams are formed with the help of applied electromagnetic fields, and finally, these beams are subjected to affected tissue from different directions. A 2-D radiation study was conducted to recreate the 2D dose distribution and use it for patient-specific IMRT quality assurance. The modified Clarkson integration approach was used to convert the log files retrieved from the Varian Unique Linear Accelerator into a 2D dose distribution.[14]

IMRT is a variant of 3D conformal radiation therapy. In comparison to 3D conformal, IMRT uses a lot smaller beams, and it is also possible to alter the power of the beams to provide larger doses to certain tumor-bearing regions.[14] An important stage in the treatment of intensity-modulated radiation is dosimetry verification. Verification is often carried out using measurements and impartial dose estimations. The usage of currently available independent dosage calculation methods for dynamic MLC beam delivery methods is inefficient because they were designed for step-and-shoot beam delivery methods. For the purpose of performing independent dose verifications for a dynamic MLC-based IMRT approach for Varian linear accelerators, a dose calculation method was created.[11]

IGRT is another variant of IMRT. Nevertheless, it also uses imaging scans while receiving radiation therapy, not just for treatment planning before sessions. The cancer patient undergoes numerous scans throughout the therapy, including CT, MRI, or PET scans. Computers analyze these scans to look for alterations in the tumor's size and location. The patient's body position/location or the radiation dose might be changed during treatment if necessary due to repeated imaging. These modifications can increase therapy precision and protect healthy tissue.[11] In cases necessitating steep dose gradients near critical organs, demanding precise dose distributions in the gastrointestinal tract with considerations for filling variations, requiring high-precision dose escalation to prevent geographic misses, and for patients experiencing challenges lying still due to pain or claustrophobia, IGRT emerges as a superior treatment method.[14,15]

Another variant of IMRT is tomotherapy which makes the use of a combination of CT scanner and external-beam radiation. In this treatment procedure, the radiation beam is delivered in a spiral pattern, slice by slice.[16] The effectiveness of tomotherapy is still a matter of concern.[17]

In stereotactic radiosurgery, tiny tumors in the brain and central nervous system with clearly defined boundaries are treated with concentrated, high-energy beams. It might be an option if surgery is not safe to do because of age, other health issues, or the location of the tumor. Stereotactic radiosurgery involves directing numerous small radiation beams from different angles toward the tumor. While each beam minimally affects the tissue it passes through, the convergence point where all beams meet receives a precisely focused dose of radiation.[18,19]

Similar to stereotactic radiosurgery, stereotactic body radiation therapy is used for small, isolated tumors that aren't in the brain or spinal cord, most frequently in the liver or lung. When you are unable to have surgery because of your age, your health, or the location of the tumor, this may be a possibility.[20]

The effectiveness of radiation therapy treatments necessitates an accurate assessment of dose distribution calculations, particularly in heterogeneous mediums and uneven surfaces. The transport equation, which is dependent on the treatment settings, the direction of the beam, the size of the radiation field, and the radiation energy, requires dose estimations in patients due to the interactions of ionizing radiation.[21]

Radiation dosimetry

Radiation dosimetry involves precisely measuring, calculating, and evaluating the ionizing radiation dose absorbed by the human body. In the context of radiation therapy, optimizing the radiation dose is a pivotal task. Various metrics are employed to quantify radiation doses, including gray (Gy) indicating energy absorbed per unit of mass (J·kg−1), equivalent dose (H) measured in sieverts (Sv), effective dose (E) also measured in sieverts, Kerma (K) in grays, dose area product in gray centimeters squared, dose length product (DLP) in gray centimeters, rads (a now deprecated unit, where 1 rad = 0.01 Gy = 0.01 J/kg), and Roentgen, a legacy unit for X-ray exposure. Despite the global adoption of the International System of Units (SI), non-SI units persist, particularly in the USA, where rads and rems are still commonly used for dose and dose equivalent, respectively. Noteworthy is the conversion where 1 Gy equals 100 rad, and 1 Sv equals 100 rem.[22]

Equivalent dose

Distinct forms of radiation, including photons, neutrons, or alpha particles, have distinct absorbed dosage thresholds

that must be reached to have a particular biological effect. The equivalent dose (H) is determined by multiplying the mean dose to the organ from a specific type of radiation by a weighting factor, which accounts for the relative biological effectiveness (RBE) of that radiation type. This takes into consideration that, for an equivalent absorbed dose in Gy, alpha particles exhibit greater biological activity compared to X or gamma radiation. The purpose of the concept of equivalent dose is to assess the stochastic risks linked with radiation exposure.[23]

Effective dose

The effective dose is the primary parameter for radiological protection, setting exposure limits to ensure that stochastic health effects are maintained below acceptable levels and tissue reactions are prevented.[23]

Radiation therapy uses ionizing radiation for cancer treatment by the way of killing cancerous cells. In addition to killing cancerous cells, ionizing radiation may damage some healthy cells nearby the treatment area. Hence, the selection of the proper dose and its frequency are very important.[23] A heavy dose of ionizing radiation may damage several healthy cells too. Hence, to effectively kill cancerous cells and simultaneously survive healthy cells, small doses at several intervals (treatment schedule) are given to the patient. This type of treatment is called fractioned treatment. Here, it is noteworthy to mention that the absorbed dose = $n.d$, where n is the number of fractioned doses and d is the dose per fraction.

Radiobiological models

Understanding the mechanism of the interaction between radiation and an organism depends heavily on the biophysical models. Numerous radiobiological models have been put out to calculate the relative biological effectiveness (RBE) and estimate the survival fraction in clinical applications.[24,25] One of the oldest theories to explain radiation-induced cell death is Lea's target theory.[26] The hit probability p_0 for hitting N targets of V volume n times, in this theory, followed a Poisson distribution, which is represented as:

$$p_0 = \left[1 - e^{-VD} \sum_{k=0}^{n-1} \frac{(VD)^k}{k!}\right]^N \quad (1)$$

To address several target theory contradictions, a linear-quadratic (LQ) model[27] has been the primary foundation for the current models used in Heidelberg, Chiba, and Hyogo, Japan. As per LQ model, cell survival (S) is:

$$S = e^{\left(-\alpha d - \beta d^2\right)} \quad (2)$$

Where $d = \left(- + \sqrt{\alpha^2 - 4 \ln S}\right) / 2$ is the dose (Gy), α and β are the radiosensitivity parameters and are determined by cell inactivation experiments *in vitro*; α is slope of cell survival curve at $d \to 0$ and β is the parameter dictating the proportion of the quadratic component's contribution.

For an n-fractioned treatment (total dose $D = n.d$), cell survival is given by:

$$S_n = e^{\left(-\alpha d - \beta d^2\right)^n} = e^{\left(-\alpha n d - \beta n d^2\right)} = e^{\left(-\alpha D - \beta D^2 / n\right)} \quad (3)$$

Further, in order to calculate relative biological effectiveness (RBE), a biologically effective dose (BED) for treatment planning in clinical applications is expressed as:

$$BED = D\left\{1 + \frac{d}{\alpha / \beta}\right\} \quad (4)$$

To forecast the radiosensitivity and cell target size and determine the BED, a generalized radiobiological model has been published.[28] This model tries to capture both direct radiation effects and effects on cellular repair. If "the cellular response after its target being hit" is a fuzzy event, the Yager negation operator can be used to express cell survival as:

$$S = \left(1 - p_0^{\alpha}\right)^{1/\alpha} \quad (5)$$

Where a is the negation parameter ($a > 0$).

Using the hit probability p_0 (eq. 1) postulated in Lea's target theory,[27] a generalized multi-hit multi-target model is proposed and thus the cell survival is expressed as:

$$S = \left[1 - \left(1 - e^{-VD} \sum_{k=0}^{n-1} \frac{(VD)^k}{k!}\right)^{Na}\right]^{1/\alpha} \quad (6)$$

A universal survival curve is also available that is basically a combination of the LQ-model curve and multi-target model asymptote.[29]

Further, a realistic probabilistic modeling is proposed for the estimation of tumor control probability (TCP). In this modeling, a fractioned treatment is used in which ionizing radiation produces killed cells (KCs), and sublethally damaged cells (SLDCs), and some of the undamaged cells (UDC). All this depends on the radiosensitivity of cells. These three types of cells can be affected by the radiation at the second and subsequent fractions. The probabilistically related mean consequences of the radiation interactions with the cells are as follows:

$$KC + SLDC + UDC = 1 \quad (7)$$

$$KC + S = 1 \quad (8)$$

Where cell survival is $S = SLDC + UDC$.

In a fractioned treatment, the likelihood of encountering one type of these cells relies on the mean number of all the cells in the sampled volume of the living tissue. Undamaged cells can experience one of three outcomes as the end consequence of radiation interactions with cellular populations: (i) Being killed, (ii) being sublethally damaged, or (iii) maintaining the status as an undamaged cell. Two first consequences are available for cells that have been sublethally injured [Figure 1]. The radiosensitivity of cells affects the likelihood of these results. In an irradiated tissue, an increase in the number of fractions results in an increase in KCs and a decrease in other types of cells.

A number of KCs, SLDCs, and undamaged cells (UDCs) arise during the first fraction of irradiating a tumor with a dose d and radiation R. The SLDCs and UDCs will contribute to an increase in the quantity of KCs in the second and succeeding fractions. The tumor is under control if, after n fractions, the number of KCs is equal to the starting number of tumor cells (TCs). TCP is determined as follows after a number of virtual simulations (NVS) using an n-fractioned treatment:

$$TCP = \frac{T|_{KC=TC}}{NVS} \quad (9)$$

Where T is the time consumed in killing all the TCs, i.e. $KC = TC$.

Multiple factors such as volume of tumor v (cm^3), cell density d (number of cells/cm^3), radiosensitivity of tumor for cell kill R_{KC} (%), radiosensitivity of cell sublethal damage R_{SLDC} (%), NVS, and number of fractioned doses N_{fd} are involved in TCP calculations, as per equation (9).

Designing the MATLAB app

In order to calculate %TCP, a MATLAB standalone app has been developed and built as follows:

Design the app

Clearly define the purpose and functionality of the app. Determine the user interface (UI) elements, data inputs, and outputs. In our case, data inputs are: volume of tumor v (cm^3), cell density d (number of cells/cm^3), radiosensitivity of tumor for cell kill R_{KC} (%), radiosensitivity of cell sublethal damage R_{SLDC} (%), NVS, and number of fractioned doses N_{fd}. The outputs are %TCP and simulation time.

Create a new app

In MATLAB, go to the "APPS" tab and click on "App Designer" to open the App Designer environment.

Design the user interface

Use the drag- and-drop interface in App Designer to design the UI of the app. Add components such as buttons, input fields, output fields, and graphics as required. Customize their properties, layout, and appearance.

Define callbacks

For interactive elements, such as buttons, define callbacks that specify the actions to be performed when these elements are interacted with. MATLAB will automatically generate callback functions to edit.

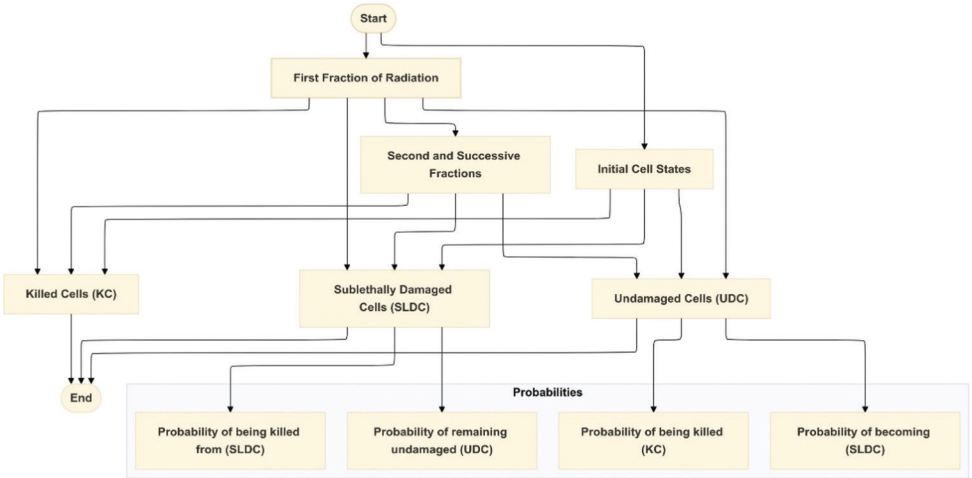

Figure 1: Illustration of the model's components and interactions between different cell states (killed, sublethally damaged, and undamaged)

Implement app logic

Write the MATLAB code that implements the functionality of the app. This code will typically be written within the callback functions or in separate functions that are called by the callbacks. Use MATLAB's extensive library of functions and toolboxes to perform calculations, data processing, plotting, etc.

Test the app

Run the app within the App Designer environment to test its functionality. Debug any errors or unexpected behavior.

Deploy the app

Once the app is functioning correctly, one can deploy it to share it with others. MATLAB provides various deployment options, including standalone applications, web apps, or integration with other platforms.

Package and distribute the app

Prepare the app for distribution by packaging it into a format suitable for sharing. This may involve creating an installer or a deployment package that includes all the necessary files and dependencies.

Share the app

Distribute the app to others by providing them with the packaged version. They can then run the app on their own machines with MATLAB installed.

RESULTS AND DISCUSSION

A TCP simulator has been developed in a MATLAB app environment. A snap of the developed app is shown in Figure 2. The simulator probabilistically describes the radiation biological effects in a tumor homogeneously irradiated with a determined dose per fraction in a fractioned treatment. In the first fraction, the mean values of killed, sublethally damaged, and undamaged cells are evaluated using the radiosensitivity characteristics of the TCs. In the second and successive fractions, the three possible kinds of cells and all possible results of interaction with radiation are probabilistically evaluated. The radiobiological effects are calculated in several virtual simulations. This enables the determination of TCP based on its own probabilistic definition, as the ratio of the simulations with no mean survived cells (i.e. mean KCs = 100%) and the total number of them. Therefore, this simulator determines the TCP through probabilistic evaluation of the radiation biological effects on the TCs in a fractioned treatment.

The simulation takes into account several key factors, including: (1) Radiosensitivity characteristics of the TCs, which determine the mean values of killed, sublethally damaged, and undamaged cells in the first fraction. (2) The three possible

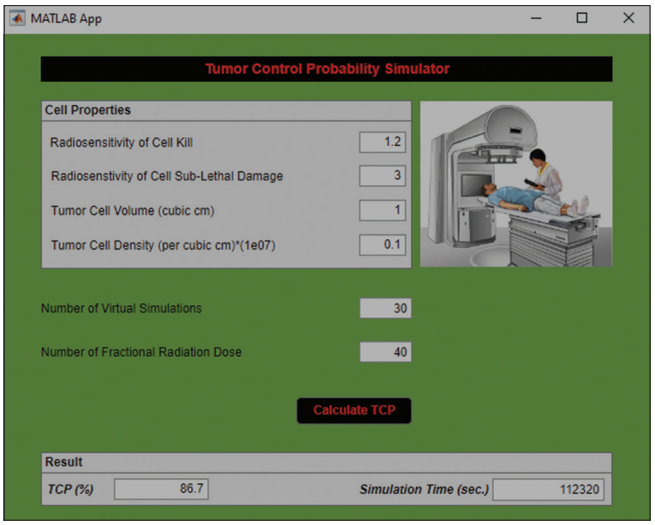

Figure 2: Snap of tumor control probability (TCP) simulator showing one set of simulation parameters and TCP percentage. TCP: Tumor control probability

kinds of cells (killed, sublethally damaged, and undamaged) and all possible results of interaction with radiation in the second and successive fractions. (3) Cell repair, which is considered a temporal process during inter-fraction. (4) Tumor volume, cell density, and number of fractions. (5) Probabilities, such as the probability of meeting a KC, of killing an undamaged cell, and of killing a sublethal damaged cell. (6) The radiation biological effects in a tumor homogeneously irradiated with a determined dose per fraction in a fractioned treatment. These factors are used to probabilistically evaluate the radiation biological effects on the TCs and determine the TCP based on its own probabilistic definition.

A snap of TCP simulator showing one set of simulation parameters and TCP percentage is shown in Figure 2. For the simulation, input parameters are radiosensitivity of cell = 1.2, radiosensitivity of cell sub-lethal damage = 3, TC volume = 1 cm^3, and TC density = 0.1×10^7, NVS = 30, and number of fractional radiation dose = 40. After simulation, the % TCP is found to be 86.7.

In order to validate the results of this simulator, we have taken data from a TC[30] characterized with α =0.258 Gy^{-1}, β =0.516 Gy^{-1}, radiosensitivity of cell = 0.7, radiosensitivity of cell sub-lethal damage = 0.3, TC volume = 5 cm^3, and TC density = 10×10^7. For this set of cell parameters, a TCP value of 60% is obtained which is in very close agreement with already published results of.[30]

The dependency of %TCP on various parameters has been checked [Figures 3-6]. Figure 3 shows the dependency of TCP% results for different values of cell kill radiosensitivity (%K). It is evident from this Figure 3 that

TCP% increases with an increase in the values of cell kill radiosensitivity (%K). Elevated radiosensitivity increases the likelihood of killing undamaged cells. This is quite obvious and illustrates positive correlations between TCP and the radiosensitivity of TCs.

Figure 4 shows variations in TCP% results for different values of number of fractional dose (N_{fd}). A larger number of fractions heighten the probability of encountering surviving cells. Again, it shows a positive correlation between TCP and the number of fractions which is very expected outcome.

Figure 5 shows TCP% results for different values of cell volume (v [cm^3]). Here, TCP% values indicate inverse relationships with volume. In the case of a large volume, the likelihood of eliminating all cells is lower compared to a smaller volume, as most cells have a higher chance of survival.

Figure 6 depicts TCP% results for different values of cell density (d [$cells/cm^3$]). High-cell density implies a greater number of cells within the same volume compared to a lower density. Again, an inverse relationships of TCP% with cell density have been observed.

The simulator illuminates favorable connections between TCP and the radiosensitivity of TCs, as well as the number of fractions, while concurrently indicating adverse correlations with volume and cell density. Augmented radiosensitivity amplifies the likelihood of eliminating intact cells. A greater number of fractions elevate the

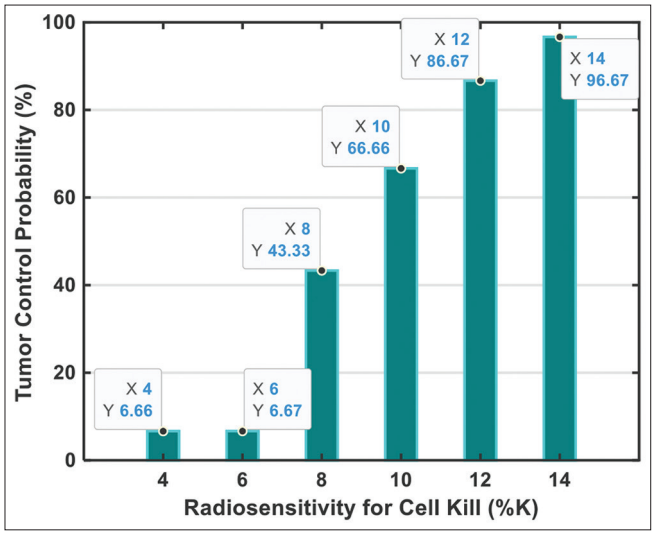

Figure 3: Tumor control probability (TCP) simulator TCP% results for different values of cell kill radiosensitivity (%K)

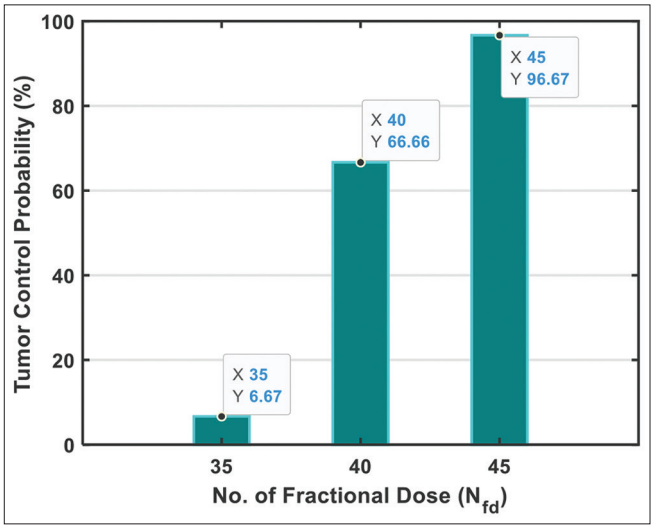

Figure 4: Tumor control probability (TCP) simulator TCP% results for different values of number of fractional dose (N_{fd})

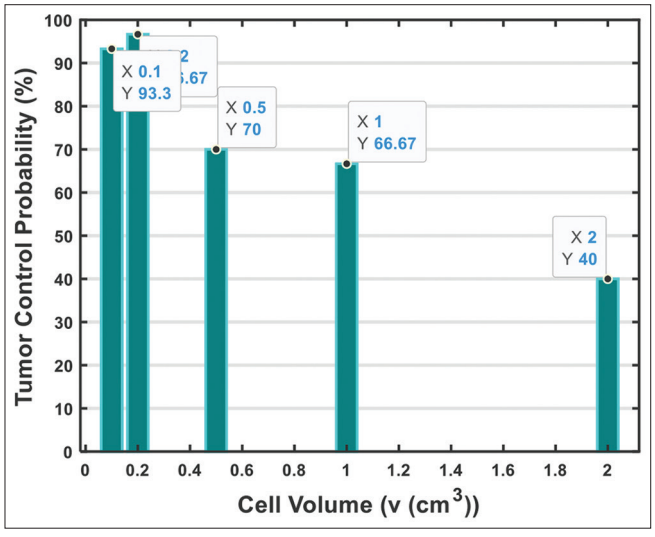

Figure 5: Tumor control probability (TCP) simulator TCP% results for different values of cell volume (v [cm^3])

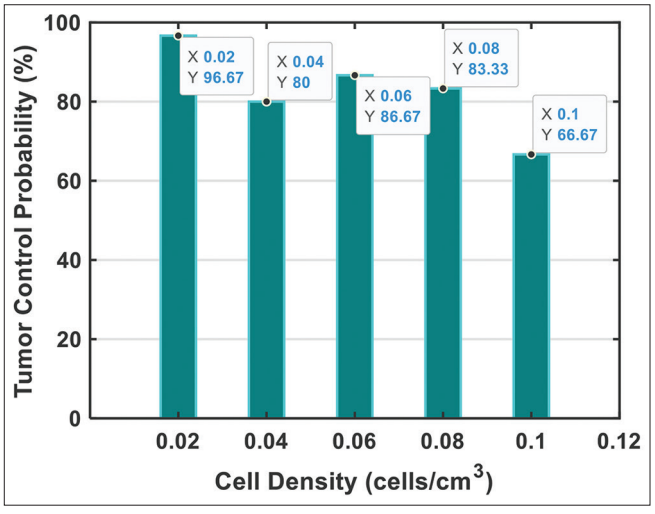

Figure 6: Tumor control probability (TCP) simulator TCP% results for different values of cell density (d [$cells/cm^3$])

probability of encountering resilient cells. In voluminous scenarios, the prospect of eradicating all cells diminishes compared to more confined settings, given the heightened likelihood of cellular survival. Elevated cell density denotes a surplus of cells within equivalent volumes relative to lower densities.

CONCLUSION

The simulator developed in this study provides a useful tool for simulating the radiation biological effects on a tumor homogeneously irradiated with the number of fractions and some amount of dose per fraction. Despite neglecting some tumor cellular processes in the first fractional dose, the simulator provides hypothesis-generating results and uses probabilistic foundations to evaluate all possible outcomes for all TCs during the second and successive fractions. The simulator determines the TCP based on its own probabilistic definition, which can be used to assess the effectiveness of fractionated radiation therapy in controlling tumor growth. The methodology used in this study could also be employed for determining radiobiological effects in normal tissues, which can generate different endpoints of an irradiated organ and/or organism, as well as other stochastic biological effects. This could have important implications for improving the safety and efficacy of radiation therapy in cancer treatment.

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Conflicts of interest
There are no conflicts of interest.

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