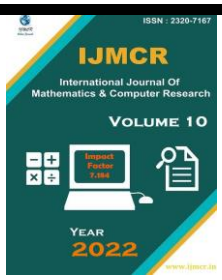
International Journal of Mathematics and Computer Research

ISSN: 2320-7167

Volume 10 Issue 08 August 2022, Page no. – 2840-2846

Index Copernicus ICV: 57.55, Impact Factor: 7.362

DOI: 10.47191/ijmcr/v10i8.03



Radiotherapy Biological Tumor Control Probability Integral Equation Model with Analytic Determination

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ARTICLE INFO

Published online:
10 August 2022

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ABSTRACT

The research objective was to obtain a fast/simple analytic solution for previously published Radiotherapy Tumor Control Probability (TCP) Integral Model by other authors. Finding, firstly, is a new/simpler Probability Function than Poisson distribution of survival clonogens which is developed from classical biological model algebraic/numerically modified equation. Solution obtained is this Probability Function alternative based on a Binomial distribution equation approximation from literature. Result, thus, is its use of for developing a fast/analytic solution of the 2D [α and β biological modelling parameters] Integral Model Cumulative TCP. The Gaussian Normal distribution convolution is implemented with this Probability Function into the integral model to sort longer/programming numerical methods and determine an analytical solution expression. As a complete result, a formulation for TCP based on Erf functions is obtained. Applications for radiotherapy treatment planning optimization improvements with biological models are explained.

KEYWORDS: Mathematical Methods (MM), Biological Models (BM), Clonogenes Population Survival Rate, (SR), Integral Equation (IE), Tumor Control Probability (TCP), Radiation Photon-Dose (RD), Nonlinear Optimization, Integral Approximations, Anisotropic Analytic Model (AAA), Radiotherapy Treatment Planning Optimization (TPO).

I. INTRODUCTION

Continuing the Radiation Therapy research series, [1-8, 17-24, 31, 32], a new Biological Models (BM) step-forward study is developed. Biological Models rationale in based on biochemistry/biomedical proven evidences [64-67] for tumor clonogenes growth and radiobiological interaction with radiation particles. Usually, BM equations are exponentials and integral equations of first kind for Tumor Control Probability (TCP) [64-67].

The objective of this research is mainly mathematical, to show, develop, and resolve the BM model variant and the modified Integral Equation Model [Casesnoves, 2022], based on significant previous literature contributions [64-67].

The Radiation Dose, usually photon dose, is set within the BM equation to obtain the optimal dose delivery. Therefore, that photon-dose magnitude can be determined in function of optimal radiobiological clonogenes population Survival Rate [N_S] and TCP to eliminate theoretically/clinically almost all clonogenes in tumor.

Thus this research presents the IE analytic determination of a classical BM [64-67]. Several new parameter forms in BM equations are presented. Approximations for TCP IE are developed based on Binomial distribution. IE analytic result formulation for the TCP model is shown. Mathematical methods and algebraic integral techniques for the research are based on previous contributions series [1-9, 17-24, 31, 32] .

Succintly, two new Biomodels are presented and mathematically developed. The first one is a $N_{[0,S]}$ variant of the classical BM equations developed in literature [64-67]. The second is a new Integral Equation Model statistically and numerically determined for analytic solution.

II. MATHEMATICAL INTEGRAL EQUATION METHOD

The starting point is the Linear Quadratic model for surviving clonogenes and the TCP basic one [64-67]. Thus, the variation of these models are introduced [Casesnoves, 2022]. Instead the Poisson TCP model, an approximation

with Binomial TCP distribution is proven [Casesnoves, 2022]. All these model variations are set into the Gaussian convolution integral equation for TCP cumulative prediction. Finally, the analytic solution for the IE is demonstrated [Casesnoves, 2022].

Linear Quadratic Model Variation-Improvement

The Linear Quadratic model equation set in [64-67] is,

$$\text{Classical Model},$$
$$N_S = N_0 \; x \; e^{-[\alpha D + \beta D^2]} \; ; \qquad (1)$$

where

Ns : Initial number of tumor clonogens
No : Surviving number of tumor clonogens
α : Clonogen radiosensitivity parameter
β : Clonogen radiosensitivity parameter
D : Total radiation dose delivered

The model can be modified for easier mathematical methods. A Lea-Catcheside function-factor K [64], has to be introduced. Fractional dose factors, d, and number of fractions n, [64-67], are omitted for simplification, and are not relevant for the mathematical method development. In the standard BM research, [64-67], the quotient [σ/β] is generally considered constant. However, for this research model IE, alpha and betha radiosensitive parameters are set independent in order to not accumulate too many approximations. By using percentages and 1% rates, the model can set better implemented in Statistical Distributions and IE, such as,

$$\text{Modified Model [\% or 1\%]},$$
$$N_S\,[\%] = N_0\,[100\%] \; x \; e^{-[\alpha D + \beta K D^2]} \; ;$$
$$\text{or}$$
$$N_S\,[1\%] = N_0\,[1\% = 1] \; x \; e^{-[\alpha D + \beta K D^2]} \; ;$$
$$[\text{Casesnoves, 2022}] \; ; \qquad (2)$$

where

Ns : Initial number of tumor clonogens
No : Surviving number of tumor clonogens
α : Clonogen radiosensitivity parameter
β : Clonogen radiosensitivity parameter
D : Total radiation dose delivered
K : Lea-Catcheside function-factor K, [64]

However, this model variant, using percentages and rates of N_0 implies to make calculations constrained to parameters [α, mainly, and β] numerical changes in function of N_0 , for example [66, Table 44.2] . In other words, both parameters [α, mainly, and β] numerical values depend on N_0 .

Probability Function Model Variation-Approximation [Casesnoves, 2022]

Thus, the next step is to use the Binomial Probability Function for TCP, which is set as an approximation at [66] and reads,

$$\text{Binomial – Approx TCP Model},$$
$$P(\alpha,\beta) = [1 - e^{-[\alpha D + \beta K D^2]}]^{N_0} \; ;$$
$$\text{Modified Rate – Model}, N_0 = 1,$$
$$P(\alpha,\beta) = [1 - e^{-[\alpha D + \beta K D^2]}] \; ; \qquad (3)$$

where

P (α , β) : Tumor Control Probability function depending on α , β

Integral Equation Approximated-Model [Casesnoves, 2022]

Probability Function (3) is convoluted in the same method of [64] with a 2D Gaussian Kernel to obtain the final cumulative TCP (α , β) distribution. The new technique is to use the Binomial approximation of (3) to reach an analytic determination. Therefore, IE reads,

$$TCP(\alpha,\beta) = \frac{1}{2\pi\sigma^2} \ldots$$
$$\ldots \int_{\beta_1}^{\beta_2} \int_{\alpha_1}^{\alpha_2} [1 - P(\alpha,\beta)] \; x \ldots$$
$$\ldots e^{\left[-\frac{1}{2\sigma^2}[(\alpha-\bar{\alpha})^2 + (\beta-\bar{\beta})^2]\right]} \ldots$$
$$\ldots d\alpha \, d\beta = I_1 - I_2 \quad ; \qquad (4)$$

where

α : Clonogen radiosensitivity integral parameter
β : Clonogen radiosensitivity integral parameter

σ : Approximated standard deviation both for α , β parameters
I_1 : First Gaussian integral, Normal Distribution
I_2 : Second Probability Function Gaussian convolution

Mathematical Algebraic-Variable Modifications

For getting to work out the analytic solution of I_2 , the following algebraic-variable changes, are applied exclusively at I_2 . A and B notation, are constants depending on D and K as described in (1-3). Note that this is not the unique algebraic-variable change. Algebraic-variable changes result be as follows,

$$(\alpha - \overline{\alpha}) \Rightarrow \left(\alpha - \left(\overline{\alpha} - \sigma^2 A\right)\right); (1)$$
$$(\beta - \overline{\beta}) \Rightarrow \left(\beta - \left(\overline{\beta} - \sigma^2 B\right)\right); (2)$$
$$\text{with complement}$$
$$+\left[\frac{\sigma^2 A^2}{2}\right] + \left[-\overline{\alpha} A\right]; \text{for (1)};$$
$$+\left[\frac{\sigma^2 B^2}{2}\right] + \left[-\overline{\beta} B\right]; \text{for (2)};$$
$$\text{where,}$$
$$A = D;$$
$$\text{and,}$$
$$B = K D^2;$$

(5)

where
α : Clonogen radiosensitivity integral parameter variable change
β : Clonogen radiosensitivity integral parameter variable change
σ : Approximated standard deviation both for α , β parameters
D: Total dose of Hypofractionated RT.

These algebraic-variable changes obtain the same IE expression than (4) and are reverted for IE Model final result formulation at I_2 . As a result, final determinations, (6-9) will be got.

I_1 and I_2 Determination

The integral I_1 is a 2D Gaussian distribution. Therefore, variable changes from (5) are not necessary. Erf functions usage for convolution integral equations is extensively presented in the mathematics literature [68]. The straightforward analytic result with Erf functions reads,

$$I_1(\alpha,\beta) = \frac{1}{4} x \left[\left[Erf\left(\frac{\alpha_2 - \overline{\alpha}}{\sqrt{2}\sigma}\right)\right] - \left[Erf\left(\frac{\alpha_1 - \overline{\alpha}}{\sqrt{2}\sigma}\right)\right]\right] ... x$$
$$... x \left[\left[Erf\left(\frac{\beta_2 - \overline{\beta}}{\sqrt{2}\sigma}\right)\right] - \left[Erf\left(\frac{\beta_1 - \overline{\beta}}{\sqrt{2}\sigma}\right)\right]\right];$$

(6)

where
α1 : Inferior 2D IE limit
α2 : Superior 2D IE limit
β1 : Inferior 2D IE limit
β2 : Superior 2D IE limit
α : Clonogen radiosensitivity integral parameter
β : Clonogen radiosensitivity integral parameter

The integral I_2 is a convolution of P (α , β) with a 2D Gaussian Kernel. Just remark that in total computation I_2 is resting for the total TCP (4). Before setting the algebraic-variables changes (5) I_2 results as follows,

$$I_2(\alpha,\beta) = \frac{1}{2\pi\sigma^2} ...$$
$$... \int_{\beta_1}^{\beta_2} \int_{\alpha_1}^{\alpha_2} \left[e^{-[\alpha D + \beta K D^2]} \right] x ...$$
$$... x\, e^{\left[-\frac{1}{2\sigma^2}\left[(\alpha-\overline{\alpha})^2 + (\beta-\overline{\beta})^2\right]\right]} ...$$
$$... x\, d\alpha\, d\beta;$$

(7)

where all parameters and constants are described in (1-6)

After applying the algebraic-variable changes (5), and for final solution reverting them, the I_2 result reads,

$$I_2(\alpha,\beta)=\frac{1}{4}x(\exp[\frac{\sigma^2}{2}(A^2+B^2)-\ldots$$
$$\ldots-(\bar{\alpha}A+\bar{\beta}B)].)..x\ldots$$
$$\ldots.x[[Erf\left(\frac{\alpha_2+(\bar{\alpha}-\sigma^2A)}{\sqrt{2}\,\sigma}\right)]-..$$
$$\ldots.-[Erf\left(\frac{\alpha_1+(\bar{\alpha}-\sigma^2A)}{\sqrt{2}\,\sigma}\right)]\,]\ldots x..$$
$$\ldots.x[[Erf\left(\frac{\beta_2+(\bar{\beta}-\sigma^2B)}{\sqrt{2}\,\sigma}\right)]-..$$
$$\ldots.-..[\ Erf\left(\frac{\beta_1+(\bar{\beta}-\sigma^2B)}{\sqrt{2}\,\sigma}\right)]]\quad ;$$

(8)

where all parameters and constants are described in (1-6)

III. INTEGRAL EQUATION MODEL RESULT [CASESNOVES, 2022]

According to all the IE model previous mathematical development, the IE analytical determination is set. The complete model analytic result, following (6,7,8) reads,

$$TCP(\alpha,\beta)=I_1(\alpha,\beta)-I_2(\alpha,\beta);$$
$$[Casesnoves\ 2022];$$

(9)

where all parameters and constants are described in (1-6).

Therefore, the model is set in function of previous determinations/approximations (1-8). The previous contributions in the Radiotherapy Treatment Planning Optimization [1-8, 17-24, 31, 32], were applied/developed for the IE model elaboration. This formula sets a cumulative TCP function $P(\alpha,\beta)$ for any parameter values $(\alpha,\beta)\in[(\alpha_1,\beta_1),(\alpha_2,\beta_2)]$.

IV. DISCUSSION AND CONCLUSIONS

The study objective was to obtain a new and fast/simple analytic solution for previously published Radiotherapy Tumor Control Probability (TCP) Integral Model by other authors [64]. Also to develop mathematically accurate approximations for the final solution.

The results show three strands. First is the Linear Quadratic model variation (2). Second is the Binomial approximated TCP distribution (3). Third is the main result, the IE analytic solution determination (6-9).

An IE model inconvenient is that the Binomial distribution approximation is constrained to a non-large number of observations. The principal IE model advantage is its analytic form for TPO fast computation and TPO numerical interval-selection for cumulative TCP.

In brief, a new group of equations and IE model analytic solution was obtained for Radiotherapy TPO with Biological models.

V. SCIENTIFIC ETHICS STANDARDS

All initial equations were developed from previous researchers contributions [64-67]. The IE initial integral formula was published in [64]. From those equations, all the mathematical development is original from the author. This article has previous papers mathematical techniques, [1-8, 17-24, 31, 32], whose use was essential to make IE model analytic solution, approximations, and Probability Function. The complete mathematical development will be carefully reviewed/checked in subsequent publications. This study was carried out, and their contents are done according to the European Union Technology and Science Ethics. Reference, 'European Textbook on Ethics in Research'. European Commission, Directorate-General for Research. Unit L3. Governance and Ethics. European Research Area. Science and Society. EUR 24452 EN [60-63]. And based on 'The European Code of Conduct for Research Integrity'. Revised Edition. ALLEA. 2017. This research was completely done by the author, the calculations, images, mathematical propositions and statements, reference citations, and text is original from the author. When a mathematical statement, proposition or theorem is presented, demonstration is always included. If any results inconsistency is found after publication, it is clarified in subsequent contributions. The article is exclusively scientific, without any commercial, institutional, academic, religious, religious-similar, non-scientific theories, personal opinions, political ideas, or economical influences. When anything is taken from a source, it is adequately recognized. Ideas and some text expressions/sentences from previous publications were emphasized due to a clarification aim [60-63].

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