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# RADBIOMOD: A simple program for utilising biological modelling in radiotherapy plan evaluation

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## *Abstract*

Purpose: Radiotherapy plan evaluation is currently performed by assessing physical parameters, which has many limitations. Biological modelling can potentially allow plan evaluation that is more reflective of clinical outcomes, however further research is required into this field before it can be used clinically.

Methods: A simple program, RADBIOMOD, has been developed using Visual Basic for Applications (VBA) for Microsoft Excel that incorporates multiple different biological models for radiotherapy plan evaluation, including modified Poisson tumour control probability (TCP), modified Zaider-Minerbo TCP, Lyman-Kutcher-Burman normal tissue complication probability (NTCP), equivalent uniform dose (EUD), EUD-based TCP, EUD-based NTCP, and uncomplicated tumour control probability (UTCP). RADBIOMOD was compared to existing biological modelling calculators for 15 sample cases.

Results: Comparing RADBIOMOD to the existing biological modelling calculators, all models tested had mean absolute errors and root mean square errors less than 1%.

Conclusions: RADBIOMOD produces results that are non-significantly different from existing biological modelling calculators for the models tested. It is hoped that this freely available, user-friendly program will aid future research into biological modelling.

Key words:

Biological modelling

Radiotherapy plan evaluation

Tumour control probability

Normal tissue complication probability

## *Introduction*

Radiotherapy plan evaluation is an essential part of the radiotherapy treatment workflow [1]. Multiple different plans can be created for individual patients that have different compromises between doses to target volumes and normal tissues. The goal of radiotherapy plan evaluation is to select the plan that has the best therapeutic ratio (high tumour control probability (TCP) and low normal tissue complication probability (NTCP)).

The current standard for evaluating radiotherapy treatment plans is the assessment of physical parameters such as dose-volume constraints on the dose-volume histogram (DVH). These parameters are used as surrogates for TCP and NTCP. The TCP is thought to be maximal if the dose-volume constraints are met for the target volume, and the NTCP is thought to be minimal if the constraints are met for the normal tissue. For example, tumour control for certain head and neck cancers may be thought to be likely if the $D_{95}$ for the planning target volume (PTV) is above 70 Gy, and radiation myelopathy thought to be unlikely to occur if the maximum dose is below 45 Gy [2]. This sole assessment of physical parameters is a very simplistic way of evaluating the adequacy of radiotherapy treatment plans, and as such, has a number of limitations.

Firstly, these constraints suggest a binary outcome – of an effect occurring or not occurring based on whether or not the constraint is achieved – when in reality the probabilities of these outcomes are continuous [3]. Secondly, a number of different DVH curves may pass through the same points, but be of markedly different shapes (e.g. curved versus step-wise) and therefore likely to be associated with different outcomes [2]. Thirdly, there are usually multiple constraints that are defined as goals for each target volume and normal tissue, and

often not all of them can be achieved simultaneously. In these situations, it is difficult to assess which would be the optimal plan to use.

Biological modelling has been proposed as a way of overcoming some of these limitations. Based on our knowledge of radiobiology, which has increased markedly over the last few decades, mathematical models have been proposed that provide metrics for estimating TCP and NTCP that may be superior to physical parameters. For example, instead of evaluating multiple physical parameters for each target volume and normal tissue, a single TCP parameter and a single NTCP parameter for each normal tissue can be evaluated. Potentially, the TCP and each NTCP can be simplified even further as a single uncomplicated tumour control probability (UTCP) metric, which can be used to rank plans [3].

While biological modelling has a lot of promise, it is still an investigational tool. There is not enough evidence yet of its predictive power to use it in routine clinical practice. Multiple reports and statements have called for more research to be made into this field so that it may one day be used in routine clinical practice [2-4]. However, research into this field is currently hampered by the complexity and inaccessibility of currently available biological modelling programs.

We have developed a simple program, RADBIOMOD, which is user-friendly and would be easily accessible for any radiation oncologist, radiation therapist, or physicist for biological plan evaluation. It provides a common platform that is not specific to any particular treatment planning system (TPS). It is hoped that by providing a user-friendly program on a common platform, more research can be made into this topic such that we may bring this closer to

routine clinical practice. The software is freely available from https://sites.google.com/site/radbiomod.

## *Methods*

### RADBIOMOD environment

Visual Basic for Applications (VBA) for Microsoft Excel was chosen as the programming language of choice to implement the biological models. This was chosen because Microsoft Excel is already readily available in most radiotherapy departments, and its basic functions should already be familiar to most radiation oncologists, radiation therapists, and medical physicists. Furthermore, the VBA code can be easily edited if the user requires the models to be customised.

RADBIOMOD requires the user to input the DVH data for the target volume or normal tissue of interest in tabular format, with dose in the first column and volume in the second column. The default DVH format that RADBIOMOD uses for calculation is differential. RADBIOMOD can also convert cumulative DVHs into differential if required. The default units are dose in Gy and volume in percentage; however other units can be easily converted or customised in RADBIOMOD. Most commercial treatment planning systems (TPS) can export the DVH in comma-separated value (CSV) or similar format, which can be copied and pasted into RADBIOMOD.

Several TCP, NTCP, equivalent uniform dose (EUD) and UTCP models were chosen for inclusion into RADBIOMOD. The mathematical equations describing each model are briefly described below. Readers are referred to the original papers for details and derivation of the equations. An example of a RADBIOMOD calculation window is shown in Fig. 1.

## TCP Models

Modified Poisson (MP) TCP model

A model for TCP derived using Poisson statistics and the linear quadratic (LQ) model has previously been described [5, 6]. This is known as the Poisson model because it assumes that the number of surviving clonogens is Poisson-distributed. This model calculates the probability of there being no viable clonogens left in the tumour after a course of radiotherapy.

In its simplest form, the number of surviving clonogens after a course of fractionated external beam radiotherapy can be described as:

$$N_S = N_0\,[\exp(-\alpha d - \beta d^2)]^N = N_0 \exp(-\alpha D - \beta D d)) \quad (1)$$

where $N_S$ is the number of surviving clonogens, $N_0$ is the initial number of clonogens, $\alpha$ and $\beta$ are LQ radiosensitivity parameters, with total dose D given homogeneously to the target over $N$ fractions, each one of dose $d$. The TCP can then be estimated using Poisson statistics as

$$TCP = \exp(-N_S) = \exp(-N_0 \exp[-\alpha D - \beta D d]) \quad (2)$$

The $N_0$ parameter can also be expressed as $\rho$, the clonogenic cell density in the target volume multiplied by the total volume of the target volume. Considering the case of heterogeneous dose distributions, we can assume the tumour volume to be composed of a series of subvolumes, $v_i$, each receiving a homogeneous dose $d_i$.

$$TCP = \prod_i \exp\left(-\rho v_i \exp\left(-\alpha D_i\left(1+\frac{\beta}{\alpha}d_i\right)\right)\right) \quad (3)$$

The population variability in radiosensitivity can also be incorporated into this model. This is simulated as a Gaussian distribution of $\alpha_j$ values with mean $\bar{\alpha}$ and standard deviation $\sigma_\alpha$.

$$g_j(\sigma_\alpha) \propto \left(\frac{1}{\sigma_\alpha \cdot \sqrt{2\pi}}\right) \cdot \exp\left(\frac{-(\alpha_j-\bar{\alpha})^2}{2\cdot\sigma_\alpha^2}\right) \quad (4)$$

$$TCP = \sum_j g_j(\sigma_\alpha) \prod_i \exp\left[-\rho v_i \exp\left(-\alpha_j D_i\left(1+\frac{\beta}{\alpha}d_i\right)\right)\right] \quad (5)$$

There have been many modifications to the Poisson TCP model. We chose a model that incorporates several additional radiobiological factors including hypoxia, radiosensitisation, and repopulation [7]

$$TCP = \sum_j g_j(\sigma_\alpha) \prod_i \exp\left[-\rho v_i \exp\left(-\alpha_j D_i \cdot SER\left(1+\frac{\beta}{\alpha}d_i \cdot SER\right) + \frac{\ln(2)}{T_{pot}}(T-T_k)\right)\right] \quad (6)$$

where *SER* is the sensitiser enhancement ratio, $T$ is the overall treatment time, $T_k$ is the kick-off time, and $T_{pot}$ is the potential doubling time.

LQ radiosensitivity parameters for hypoxic (H) and aerobic (A) cells can be determined through the following relations [8]:

$$\alpha_H = {}^{\alpha_A}/_{OER} \tag{7}$$

$$\left({}^{\alpha}/_{\beta}\right)_H = \left({}^{\alpha}/_{\beta}\right)_A \cdot OER \tag{8}$$

where OER is the oxygen enhancement ratio.

The overall TCP can be calculated based on dividing the cells into a hypoxic fraction (HF) and an aerobic fraction (1 – HF), and then calculating the TCP for each group, using the hypoxia-modified radiosensitivity parameters described in equations (7) and (8) [7]:

$$TCP = TCP_H(HF) + TCP_A(1 - HF) \tag{9}$$

The above equation does not distinguish between the differing doses received by hypoxic and non-hypoxic regions. This should be used when the geographic location of hypoxia is unknown. When hypoxia imaging (for example, $^{18}$F-fluoromisonidazole PET) is performed, and the geographic location of hypoxia is known, the gross tumour volume (GTV) should be split into a hypoxic GTV ($GTV_H$) (as defined by the hypoxia imaging) and a non-hypoxic GTV ($GTV_A$) (derived by performing a Boolean subtraction of $GTV_H$ from GTV on the TPS). The overall TCP can then be calculated by finding the product of the TCPs for each volume:

$$TCP = TCP_H(GTV_H) \cdot TCP_A(GTV_A) \tag{10}$$

The main limitation of the Poisson TCP model is that the TCP for protracted treatments has been shown to be non-Poissonian because of cell proliferation between fractions [9].

However, other studies have shown that in the condition of a small surviving fraction and a large number of clonogens, the distribution does still converge to the Poisson distribution, and as such the Poisson models do still fit reasonably well to experimental data [9].

Modified Zaider-Minerbo (MZM) TCP model

A model for TCP derived using the theory of birth-and-death stochastic processes was originally described by Zaider and Minerbo [10]. The mathematics behind this model is thought to be more accurate than the Poisson models [9]. This was later adapted for the case of fractionated delivery with varying time intervals between fractions and heterogeneous dose distributions [11, 12]. We have incorporated the concept of kick-off time into this model:

$$TCP = \prod_i TCP(D_i, v_i) \tag{11}$$

$$TCP(D_i, v_i) = \left[1 - \frac{p_s(T_n)e^{\lambda T_n}}{\left(1 - p_s(T_n)e^{\lambda T_n}\sum_{j=1}^{n-1}\frac{1}{p_s(T_j)}\left[e^{-\lambda t(T_{j+1})} - e^{-\lambda t(T_j)}\right]\right)}\right]^{\rho v_i} \tag{12}$$

$$p_s(T_j) = exp\left(-\alpha\left(\frac{j}{n}D_i\right) - \frac{\beta\left(\frac{j}{n}D_i\right)^2}{j}\right) \tag{13}$$

$$t(T_j) = \frac{T_j - T_k + |T_j - T_k|}{2} \tag{14}$$

where $n$ is the number of fractions, $\lambda$ is the rate of cellular repopulation, $T_j$ is the time between the *jth* fraction and the first fraction, $T_k$ is the kick-off time, $t(T_j)$ is the number of

days $T_j$ is beyond $T_k$, and $\rho$ is the clonogenic cell density. $p_s(T_j)$ is the cell survival after the *jth* fraction, as predicted using the linear-quadratic model, where $\alpha$ and $\beta$ are radiosensitivity parameters, and $D_i$ is the total dose delivered to a subvolume, $v_i$.

The MZM model is relatively simplistic and does not take important radiobiological factors such as hypoxia and cell cycle effects into consideration. However, this model can easily be modified to include these factors.

## NTCP models

Lyman-Kutcher-Burman (LKB) NTCP model

Emami et al. published a seminal paper in 1991 [13], describing the tolerance dose values for 28 critical structures, which provided the framework for much of the modern research into normal tissue tolerances. Burman [14] fit the tolerance dose data from that paper into a phenomenological NTCP model proposed by Lyman [15]. Kutcher and Burman [16] later developed a method for DVH reduction that could take heterogeneous dose distributions into account. The combined formalism is often referred to as the LKB model. A mathematically equivalent but clearer formulation of the LKB model has been proposed [17-19], consisting of three equations:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \tag{15}$$

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}} \tag{16}$$

$$D_{eff} = \left(\sum_i v_i D_i^{1/n}\right)^n \quad (17)$$

where $D_{eff}$ is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual non-uniform dose distribution, and $D_i$ is the dose given to a subvolume, $v_i$. This model has three parameters: $n$, $m$ and $TD_{50}$. The volume dependence of the complication probability is given by $n$ and the slope of the complication probability vs dose curve is given by $m$. $TD_{50}$ is the dose to the whole organ that would lead to a complication probability of 50%.

Biological dose adjustment is sometimes considered in the LKB model. This is an important consideration because dose heterogeneity in normal tissues will have biological effects due to the varying fraction sizes as well as total dose. [6] Furthermore, where fraction sizes other than 2 Gy per fraction are used, the unadjusted "physical" DVH may not be reflective of biological effect. This can be accounted for by calculating the equivalent dose in 2 Gy per fraction ($EQD_2$) for each dose bin as follows:

$$EQD_2 = D_i \cdot \frac{\alpha/\beta + d_i}{\alpha/\beta + 2} \quad (18)$$

where $D_i$ is the total dose received by the dose bin and $d_i$ is the dose-per-fraction received by the dose bin. This adjusted DVH can then be applied to the LKB equations as described above.

By default, all of the parameters listed in Table 1 are available for the user to select in RADBIOMOD. The user is free to edit these values or enter completely new ones to be saved in RADBIOMOD.

There are two main limitations of the LKB model. Firstly, not all of the parameters have been updated, and as such, many of them are still based on Emami estimates [13], the accuracy of which have been criticised [20]. Secondly, the method of DVH reduction employed can result in different NTCP estimates for the same data and same parameters [20].

## EUD models

EUD

The EUD is defined as the biologically equivalent dose that if given uniformly, will lead to the same biological effect as the actual nonuniform dose distribution [21]. It can be applied to both tumours and normal tissues. It is described by the following formula [22]:

$$EUD = (\sum_i v_i D_i^a)^{\frac{1}{a}} \quad (19)$$

where the dose, $D_i$ is delivered to a subvolume, $v_i$, and $a$ is a unitless model parameter that is specific to the normal structure or tumour of interest.

The TCP and NTCP can be calculated from the EUD using the following formulae [22]:

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (20)$$

$$NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (21)$$

where the $TCD_{50}$ is the tumour dose required to control 50% of the tumours when the tumour is homogeneously irradiated, the $TD_{50}$ is the normal tissue dose that would lead to a complication probability of 50% if the normal tissue is homogeneously irradiated, and the $\gamma_{50}$ is a unitless model parameter that is specific to the normal tissue or tumour of interest and describes the slope of the dose-response curve.

## UTCP

The UTCP is the probability of controlling a tumour without causing normal tissue complications. In its simplest form, it is given using the following formula:

$$UTCP = TCP \cdot (1 - NTCP) \quad (22)$$

defined using the TCP for a tumour and the NTCP for a single nearby organ.

This was modified by Agren et al. [23] to include a correlation parameter, $\delta$ to describe the fraction of patients where tumour control and normal tissue complications are statistically independent and where multiple normal tissues can be accounted for using the following formulae:

$$UTCP = TCP - P_I + \delta P_I(1 - TCP) \quad (23)$$

$$P_I = 1 - \prod_{i=1}(1 - NTCP_i) \quad (24)$$

where $P_I$ is the probability of injury to each normal tissue of interest, *i*.

The UTCP model makes the assumption that gains in TCP are of equal value to drops in NTCP without consideration of the clinical importance of the endpoints that are being estimated. Clearly, a small gain in TCP would not offset a small rise in the risk of an unacceptable toxicity such as myelopathy. Furthermore, if there are errors in the underlying TCP or NTCP functions, the UTCP would also be inaccurate [24]. As such, until these models are improved, clinical judgement must still be used rather than relying purely on this metric to rank the plans.

## Validation of calculations

The accuracy of the biological modelling calculations in RADBIOMOD were validated by comparing them to the same calculations performed on other biological modelling programs using sample clinical cases.

The biological modelling programs selected for comparison include XiO 4.70 (Elekta, Stockholm, Sweden), CERR [25], EUDMODEL [22], and TCP_NTCP_CALC [12]. XiO was selected because its biological models (MP TCP and LKB NTCP) are well described, the models are similar to those used in RADBIOMOD, and is widely used as a clinical TPS.

CERR was chosen because it has the ability to calculate LKB NTCP using similar calculations as in RADBIOMOD, and is freely available. EUDMODEL and TCP_NTCP_CALC were chosen because they were created by the authors of the EUD TCP/NTCP and MZM TCP models, respectively and to our knowledge are the only available calculators for these models.

15 sample cases were randomly selected from recently treated clinical cases in our department. These patients consisted of five patients with head and neck malignancies, treated with curative-intent radiotherapy to 70 Gy in 35 fractions using IMRT techniques; five patients with prostate cancer, treated with curative-intent radiotherapy to 78 Gy in 39 fractions using IMRT techniques; and five patients with lung cancer, treated with curative-intent radiotherapy to a dose of 60 Gy in 30 fractions using 3D-conformal techniques.

MP TCP was calculated on RADBIOMOD and XiO for five head and neck cancer patients and five prostate cancer patients. The following parameters were used for head and neck cancer: $\alpha = 0.40\ Gy^{-1}$, $\sigma_\alpha = 0.07\ Gy^{-1}$, clonogenic cell density = $10^7$ clonogens/cm$^3$, kick-off time ($T_k$) = 28 days, potential doubling time ($T_{pot}$) = 3 days [7]. The following parameters were used for prostate cancer: $\alpha = 0.26\ Gy^{-1}$, $\sigma_\alpha = 0.06\ Gy^{-1}$, clonogenic cell density = $10^6$ clonogens/cm$^3$ [26], no kick-off time, and potential doubling time ($T_{pot}$) = 42 days [27]. The $\beta$ term was not used in these calculations, as it is not available in XiO due to the assumption that its effects are minimal where 2 Gy per fraction is used and the tumour has a high $\alpha/\beta$ ratio.

MZM TCP was calculated on RADBIOMOD and TCP_NTCP_CALC for five head and neck cancer patients and five prostate cancer patients. The following parameters were used for

head and neck cancer: $\alpha = 0.396\ Gy^{-1}$, $\beta = 0.0396\ Gy^{-2}$, clonogenic cell density = $10^7$ clonogens/$cm^3$, and $\lambda = 0.231$ [7]. The following parameters were used for prostate cancer: $\alpha = 0.26\ Gy^{-1}$, $\beta = 0.0312\ Gy^{-2}$, clonogenic cell density = $10^6$ clonogens/$cm^3$ [26], and $\lambda = 0.0165$ [27]. The kick-off time was not used in these calculations.

LKB NTCP was calculated on RADBIOMOD, XiO, and CERR for the parotids for five head and neck cancer patients and for the lungs for five lung cancer patients. The following parameters were used for the parotids: TD50 = 31.4 Gy, n = 1, m = 0.53 [19]. The following parameters were used for the lungs: TD50 = 31.4 Gy, n = 1, m = 0.45 [2]. Corrections for dose-per-fraction were not used as this feature is not available in XiO or CERR.

EUD TCP was calculated on RADBIOMOD and EUDMODEL for five head and neck cancer patients and five prostate cancer patients. The following parameters were used for head and neck cancer: TCD50 = 64.9 Gy, $\gamma_{50} = 3.2$, and a = -13 [22, 28, 29]. The following parameters were used for prostate cancer: TCD50 = 70.5, $\gamma_{50} = 2.9$, and a = -24 [30, 31].

EUD NTCP was calculated on RADBIOMOD and EUDMODEL for the parotids for five head and neck cancer patients and for the lungs for five lung cancer patients. The following parameters were used for the parotids: TD50 = 31.4, a = 1, $\gamma_{50} = 2$ [19, 22]. The following parameters were used for the lungs: TD50 = 31.4, a = 1, $\gamma_{50} = 2$ [2, 22].

## Ethical approval and statistical analyses

The Austin Health Human Research Ethics Committee granted approval for this study. The biological modelling calculation results with RADBIOMOD were compared with those performed on the comparison programs by mean average error (MAE) and root mean square error (RMSE) [32]. The differences between RADBIOMOD and the comparison programs were defined as being non-significant if the MAE and RMSE were less than 1%.

## *Results*

TCP and NTCP results for each of the sample cases are shown in Tables 2 and 3, respectively.

There were non-significant differences between RADBIOMOD and XiO for the MP TCP model. The TCPs of the five prostate cancer patients had MAE and RMSE values of 0.25% and 0.31%, respectively, while the TCPs of the five head and neck cancer patients had MAE and RMSE values of 0.06% and 0.06%, respectively.

There were non-significant differences between RADBIOMOD and XiO for the LKB NTCP model. The parotid NTCPs of the five head and neck cancer patients had MAE and RMSE values of 0.18% and 0.21%, respectively, while the lung NTCPs for the five lung cancer patients had MAE and RMSE values of 0.03% and 0.06%, respectively.

There were non-significant differences between RADBIOMOD and CERR for the LKB NTCP model. The parotid NTCPs of the five head and neck cancer patients had MAE and RMSE values of 0.49% and 0.55%, respectively, while the lung NTCPs for the five lung cancer patients had MAE and RMSE values of 0.02% and 0.03%, respectively.

There were no differences between RADBIOMOD and EUDMODEL for both the EUD TCP model and the EUD NTCP model. The EUD TCP was tested for five prostate cancer patients and five head and neck cancer patients; and the EUD NTCP was tested for the parotids for five head and neck cancer patients and the lungs for five lung cancer patients. The results were identical, with MAE and RMSE being 0% for all comparisons.

Similarly, there were no differences between RADBIOMOD and TCP_NTCP_CALC for the MZM TCP model. The TCP was tested for five prostate cancer patients and five head and neck cancer patients. The results were identical, with MAE and RMSE being 0% for all comparisons.

## *Discussion*

We have developed a program for using biological models to evaluate radiotherapy treatment plans that we have fully described and successfully validated with existing biological modelling programs.

Because RADBIOMOD contains features not included in other programs, some of the features could not be validated. For example, RADBIOMOD's MP TCP model includes a β parameter, hypoxia, and sensitiser enhancement, none of which are included in XiO, so were not tested.

The comparisons between the models tested in XiO and CERR as compared with RADBIOMOD indicated that differences were very small, however the numbers were not identical. Some of the small variations that arose were likely due to the way the DVH data is used by the various programs. XiO and CERR perform calculations using the radiotherapy

planning data, whereas RADBIOMOD performs calculations using exported DVH tables. Differences in DVH binning may be a source of error. In contrast, EUDMODEL and TCP_NTCP_CALC produce identical results to RADBIOMOD, probably because they also use exported DVH tables and have identical algorithms. The random number generator used in the MP TCP model may be a further source of error in that model.

Interestingly, the results varied significantly between the MP TCP model, the MZM TCP model, and the EUD TCP model; and also between the LKB NTCP model and the EUD NTCP model. This could be due to the fact that the model parameters were selected from a number of different sources, and many of them have not been clinically validated.

RADBIOMOD is an extra addition to a range of biological modelling programs that are already available, including BIOPLAN [6], TCP_NTCP_CALC [12], CERR [25], SABRE [33], and EUDMODEL [22]. Similar to these programs, RADBIOMOD can perform calculations using a variety of biological models. However, RADBIOMOD also has several features that make it unique. Its strongest feature is the Microsoft Excel environment, which should be familiar and therefore easy to learn for most radiation oncologists, radiation therapists, and medical physicists. This environment allows easy manipulation of data, including situations where the DVH output from the TPS needs to be changed into a format that RADBIOMOD recognises. The VBA code can also be easily customised to the user's needs, for example if the user would like to add an extra parameter to any of these models. Furthermore, the calculation time is very quick, allowing the rapid evaluation of multiple treatment plans. These features make RADBIOMOD ideally suited for research into the clinical validation of biological models or planning studies using novel radiotherapy techniques [34, 35].

At this stage, RADBIOMOD is purely a research tool, and we do not recommend its use in routine clinical practice. Biological modelling in general still has a number of limitations that require further improvements before it can be used clinically. For example, a wide range of different models and model parameters are available, and all of them give slightly different results. Most models and parameters have not been prospectively validated with clinical data [3]. Models and parameters published by other groups may have fundamental differences that limit their use in the local setting. For instance, differences in treatment technique (3D-CRT vs IMRT, different beam angles, etc) or differences in patient characteristics (demographics, comorbidities, etc) may limit their generalisability [3]. This limitation could potentially be overcome if institutions derived their own biological model parameters based on their own experiences [3].

Despite these current limitations, the potential for biological modelling is immense. It is widely recognised that physical parameters for plan evaluation are mere surrogate measures of biological responses, and these should be replaced by biological indices in order for the treatment process to more closely reflect the clinical goals of radiotherapy [3, 4].

## *Conclusion*

RADBIOMOD makes multiple biological models available in a user-friendly and familiar format. It produces results that are non-significantly different from existing biological modelling calculators for the models tested. It is hoped that this freely available, user-friendly program will aid future research into biological modelling.

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Figure 1. LKB NTCP calculation window