# Radiation treatment dose optimisation using Poisson tumour control probability parameters

**G A Cho[1,2], M A Ebert[3,4], L Holloway[2,5], Z Kuncic[2], C Baldock[6] and D I Thwaites[2]**

[1]Department of Radiation Oncology, Royal Prince Alfred Hospital, Sydney Local Health District, Camperdown, NSW, Australia
[2]Institute of Medical Physics, School of Physics, University of Sydney, Sydney, NSW, Australia
[3]Radiation Oncology Department, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA, Australia
[4]School of Physics, University of Western Australia, Crawley, WA, Australia
[5]Liverpool and Macarthur Cancer Therapy Centres, Sydney South Local Health District, Liverpool, NSW, Australia
[6] Faculty of Science, Macquarie University, Sydney, NSW, Australia

E-mail: gwi.cho@sswahs.nsw.gov.au

**Abstract**. This study examines the Poisson tumour control probability (TCP) $\gamma_{37}$ and $D_{37}$ parameters of a uniformly irradiated numerical tumour model using changes in tumour burden as a surrogate for treatment response information. An optimum dose $D_i$ for a tumour sub-volume element $V_i$ is described that maximizes TCP as a function of fixed tumour integral dose $\xi$. TCP was calculated for spatially-varying clonogen density for a total $10^8$ cells and radiosensitivity $\alpha$ with mean radiosensitivity in the range $0.4 – 1.0$ $Gy^{-1}$. A bivariate normal distribution is used to describe the radiosensitivity $\alpha$ and the linear term of the linear-quadratic (LQ) cell kill governed the changes in the regional tumour burden within sub-volumes $V_i$. The optimum dose distribution, $D_i$, for $V_i$ is obtained as a function of fixed tumour integral dose $\xi$. For a uniform dose delivery and for TCP = 37%, $\gamma_{37}$ and $D_{37}$ are described by the effective radiosensitivity $\alpha_{eff}$ and the effective clonogen number $N_{0,eff}$, respectively. $\alpha_{eff}$ is equivalent to differential dose changes in the number of clonogenic cells (tumour burden). The $\gamma_{37}$ values were found to be inversely correlated with variance of the probability density function of the $\alpha$ distribution. For the biologically optimum dose distribution, $\gamma_{37}$ was found to converge to the theoretical maximum limit and $D_{37}$ was found to reduce relative to that obtained for the uniform dose case. The TCP parameters $\gamma_{37}$ and $D_{37}$ could thus be useful in optimising individual radiation treatment doses even when tumour heterogeneity is taken into account.

## 1. Introduction

With the availability of functional and molecular imaging modalities such as Positron Emission Tomography (PET), the acquisition and application of tumour specific, *in vivo* biological information to routine radiation treatment has become feasible. Biologically guided radiation treatment aims to achieve biological conformity of the dose distribution within tumour regions of higher recurrence risks to maximize the probability of local tumour control [1, 2].

A validated biological response model can be used as an objective function for dose optimization of intensity modulated radiation treatment (IMRT), whereby the search for the optimum dose distribution can be directly based on treatment response to radiotherapy [3]. While experimental

biological data are lacking, the effect on treatment response of intra-tumour biological heterogeneity has nevertheless been investigated in several theoretical modeling studies using tumour control probability (TCP) [4, 5, 6]. These studies showed that the variation of the radiosensitivity parameter $\alpha$ has a dominant influence on the TCP and dose response parameters.

In this study, the biological consequence of intra-tumour biological heterogeneity was studied under both uniform and biologically optimum (i.e. maximal TCP) dose distributions using the standard linear-quadratic (LQ) cell survival and mechanistic Poisson TCP models [3, 7]. These models were chosen for the current investigation due to their extensive application to radiation treatment response modeling and dose optimization studies. For uniform dose distribution, the steepness and the position of TCP curves were evaluated quantitatively with normalized dose gradient $\gamma_{37}$ and the dose required to achieve 37% of tumour control, $D_{37}$. The normalized dose gradient $\gamma$ is a relative measure of increase in TCP per given increment in dose. For Poisson TCP model, the steepest point of dose response curve is located at the 37% response level and, $\gamma_{37}$ is a function of number of (effective) clonogenic cells. Using the steepest part of the Poisson TCP curves and $\gamma_{37}$ and $D_{37}$ parameters, the aim was to evaluate quantitatively, the effect on the dose response curve of the biologically optimum dose distribution, in relation to the optimization criterion applied (TCP maximization) and also against the uniform dose cases as the reference. The relationship between tumour burden and $\gamma_{37}$ and $D_{37}$ parameters was investigated. The optimum dose distribution that maximizes TCP for a given fixed tumour integral dose $\xi$, was described and the gain in TCP from a biologically optimized dose distribution was quantified in terms of $\gamma_{37}$ and $D_{37}$ parameters.

## 2. Methods and materials

### 2.1. Poisson TCP and LQ cell survival models
It was assumed that a tumour is a parallel structure and is curable only if there is no surviving clonogen remaining after treatment [8]. For a discretized tumour model consisting of a group of $M$ independent sub-volume elements (with the $i$-th element having volume $V_i$), the TCP is described by

$$TCP(V_1 + V_2, \ldots, V_M) = \prod_M TCP_M \tag{1}$$

where $TCP_M = \exp(-N_M)$ is the probability of finding zero surviving clonogenic cells when the expected mean number of clonogenic cells is $N_M \neq 0$. The radiation response of tumour cells is described by the linear term of the LQ cell survival model [5]; for element $M$ with local radiosensitivity, $\alpha_M$, and surviving number of cells, $N_M$, after dose $D_M$, is $N_M = N_{M,0} \cdot \exp(-\alpha_M D_M)$, where $N_{M,0}$ was the initial number of clonogenic cells. The TCP curve was parameterized as a function of $\gamma_{37}$ and $D_{37}$ parameters [9].

### 2.2. Optimum dose distribution
The optimum dose distribution that maximizes TCP was investigated using the Lagrange multiplier method. The objective was to find the maximum TCP under the constraints of fixed integral dose to a tumour. The objective function $F$ was defined as the log of the TCP:

$$F(D_1, \ldots, D_M) = \sum_{i=1}^{M} -\left(N_{i,0} \cdot e^{-\alpha_i D_i}\right) \tag{2}$$

where $N_{i,0}$ is the initial number of clonogenic cells, $\alpha_i$ is the radiosensitivity and $D_i$ is the biologically optimum dose calculated for the $i$-th tumour element. The constraint of the fixed integral dose to a tumour is met if $\sum_{i=1}^{M} D_i - \xi = 0$, where $\xi$ is the tumour integral dose. The constraint function $\phi$ is defined as:

$$\phi(D_1, \ldots, D_M) = \sum_{i=1}^{M} D_i - \xi = 0 \tag{3}$$

We define the auxiliary function $G$ as:

$$G(D_i,\ldots,D_M,\lambda) = \sum_{i=1}^{M} -\left(N_{i,0}\cdot e^{-\alpha_i D_i}\right) + \lambda\left(\sum_{i=1}^{M} D_i - \xi\right) \qquad (4)$$

where $\lambda$ is the Lagrange multiplier. Taking the partial derivative of $G$ with respect to $D_i$, we can apply the multiplier condition:

$$\frac{\partial G}{\partial D_i} = \alpha_i N_{i,0} e^{-\alpha_i D_i} + \lambda = 0 \qquad (5)$$

*2.3. Tumour model*

A numerical tumour model consisting of $2^{10}$ elements was generated in MATLAB$^{®}$. Each element of the tumour model was described by the number of clonogenic cells $N$ and the mean radiosensitivity parameter $\alpha$. The clonogenic cells were distributed across four consecutive transverse planes with each plane consisting of $2^{8}$ tumour elements. The clonogenic cell distribution was set to have a uniform higher clonogenic cell concentration at the core and exponentially decreasing density towards the edge of the tumour model:

$$\rho(r) = N_n \qquad\qquad r \le r_{0,n}$$
$$= N_n\cdot\exp(-r/3.2) \quad r > r_{0,n}$$
$$n = 1,2,3,4 \qquad\qquad\qquad\qquad (6)$$

with $r_{0,1} = r_{0,4} = 0.45$ cm and $r_{0,2} = r_{0,3} = 0.72$ cm, respectively. For each transverse plane, $N_n$ was set to obtain $2\times10^7$, $3\times10^7$, $3\times10^7$ and $2\times10^7$ cells, resulting in total $10^8$ clonogenic cells.

The radiosensitivity of human tumours is difficult to determine *in vivo* [10]. Currently no known molecular imaging modality can directly provide spatial intra-tumour radiosensitivity distribution *in vivo* [11]. With limited information on the true distribution of radiosensitivity, $\alpha$ was described by a randomly distributed bivariate normal distribution [12], as follows:

$$\alpha_{mn} = \alpha(x_m, y_n) = \alpha_{mean}\cdot c_{normal}\cdot p_{normal}(x_i, y_j) \qquad (7)$$

$$p_{normal}(x_i, y_j) = \frac{1}{2\pi\sigma_x\sigma_y}\exp\left[-\frac{(x_i-\bar{x})^2}{2\sigma_x^2} - \frac{(y_j-\bar{y})^2}{2\sigma_y^2}\right] \qquad (8)$$

where $c_{normal}\cdot\langle p_{normal}(x_i, y_j)\rangle = 1$. With equal variance and zero co-variance terms, the probability density function provided a basic form of normally distributed α distributions that can be mapped on the clonogenic cell distribution. A 1-D Gaussian alpha distribution was applied to the LQ cell survival and Poisson TCP models of the same mathematical forms [6]. The variance parameters $\sigma_x^2 = \sigma_y^2 = 10.0$ and 11.0 were chosen to yield the coefficient of variation in surviving fraction at 2 Gy to be between 10 - 15% [13] for $\alpha_{mean} = 0.4$ and less than 30% at $\alpha_{mean} = 0.8$ and were used with mean radiosensitivity $\alpha_{mean} = 0.4 – 1.0$ Gy$^{-1}$. Ten series of $p_{normal}(x_i, y_j)$ were generated for each variance parameter to calculate the corresponding TCPs.

**3. Results and discussion**

*3.1. Biologically optimum dose distribution*

The equation for biologically optimum $D_i$ distribution was obtained as a function of fixed tumour integral dose $\xi$ from equation (5).

$$D_i = \frac{\beta + \ln(\alpha_i N_{i,0})}{\alpha_i} \tag{9}$$

$$\beta = -\ln(-\lambda) = \left[ \xi - \sum_{i=1}^{M} \ln(\alpha_i N_{i,0}) \cdot \alpha_i^{-1} \right] \left( \sum_{i=1}^{M} \alpha_i^{-1} \right)^{-1} \tag{10}$$

*3.2. TCP $\gamma_{37}$ and $D_{37}$ parameters for uniform and biologically optimum dose distribution*

For a uniform dose delivered to the non-uniform model tumour, the TCP $\gamma_{37}$ and $D_{37}$ parameters were defined by $\gamma_{37} = \ln N_{0,\text{eff}} \cdot e^{-1}$ and $D_{37} = e \cdot \gamma_{37} \cdot (\alpha_{\text{mean}})^{-1}$ respectively. $N_{0,\text{eff}}$ is the effective clonogenic cell number and $\alpha_{\text{eff}}$ is the effective radiosensitivity, which is the differential dose change in the number of clonogenic cells at TCP = 37%. $N_{0,\text{eff}}$ is a function of $\alpha_{\text{eff}}$ and $D_{37}$ at TCP = 37% . Figure 1 shows the variation of mean $\alpha_{\text{eff}} \cdot (\alpha_{\text{mean}})^{-1}$ for the uniform dose delivery. Tables 1 and 2 show averages of ten TCP $\gamma_{37}$ and $D_{37}$ parameters, $\gamma_{37,\text{mean}} = \sum_{k=1}^{10} \gamma_{37,k} / 10$ and $D_{37,\text{mean}} = \sum_{k=1}^{10} D_{37,k} / 10$ for the uniform and biologically optimum dose distributions for a tumour mean dose of 90 Gy (and with fixed tumour integral dose).

Tumours with higher heterogeneity in radiosensitivity (lower variance parameter, $\sigma_x^2 = \sigma_y^2$), exhibit lower $\gamma_{37,\text{mean}}$ values, which are also below the theoretical limit of $6.777 = \ln 10^8 \cdot e^{-1}$. $\gamma_{37,\text{mean}}$ values are largely insensitive to variations in $\alpha_{\text{mean}}$ and correlate inversely with the coefficient of variation of the α distribution (results not shown). $D_{37,\text{mean}}$ decreases with higher $\alpha_{\text{mean}}$ and $\sigma_x^2 = \sigma_y^2$. For the biologically optimum dose distribution, $\gamma_{37,\text{mean}}$ converges to the maximum theoretical limit. Negligible differences in $\gamma_{37,\text{mean}}$ were found between $\sigma_x^2 = \sigma_y^2 = 10.0$ and 11.0. A similar observation was made for $D_{37,\text{mean}}$ (0.5%) (cf. 4.5% for uniform dose case).

In this study, a range of $\alpha_{\text{mean}}$ values have been considered up to 1.0 Gy$^{-1}$ as an upper limit. For a tumour with a majority of clonogens consisting of a highly radiosensitive population (e.g. $\alpha_{\text{mean}} = 1.0$ Gy$^{-1}$), the tumour control could be dominated by the small number of radioresistant sub-population of cells. If this were the primary cause of radiation treatment failure for a given tumour, the current dose optimization (dose redistribution) approach may enable more efficient use of radiation dose to control the regions of high resistance to achieve the optimum tumour control.

An earlier study by Yang and Xing [14] explored an IMRT dose optimization framework incorporating spatial biology distribution using LQ cell survival and Poisson TCP models. The current study investigated a similar question but with a different approach in that the dose prescription was derived as an implicit function of tumour integral dose. In the current approach, the intermediate step that was needed to correlate the reference voxel dose with a voxel dose in question is no longer required. This study also evaluated the effect of uniform and biologically optimised dose distributions using a plan quality indicator, the Poisson TCP at 37% of tumour control, instead of dose volume criteria [14].

Further work is required to incorporate the effect on TCP of uncertainty in the radiosensitivity parameter estimation and to use the realistic (deliverable) dose model that results from biologically optimum dose prescription $D_i$.

## 4. Conclusion

For a heterogeneous tumour treated with a uniform radiation dose, TCP = 37% can be adequately described with parameters $\gamma_{37}$ and $D_{37}$ analogous to those employed for a homogeneous tumour, by introducing an effective radiosensitivity $\alpha_{\text{eff}}$ and an effective clonogen number $N_{0,\text{eff}}$. The parameter $\alpha_{\text{eff}}$ is equivalent to differential dose changes in the number of clonogenic cells, which could potentially be determined experimentally. For a heterogeneous tumour treated with a biologically optimized dose distribution, on the other hand, $\gamma_{37}$ is maximized, while $D_{37}$ is reduced. These results suggest that the Poisson TCP parameters $\gamma_{37}$ and $D_{37}$ could be useful in optimizing individual radiation treatment doses.
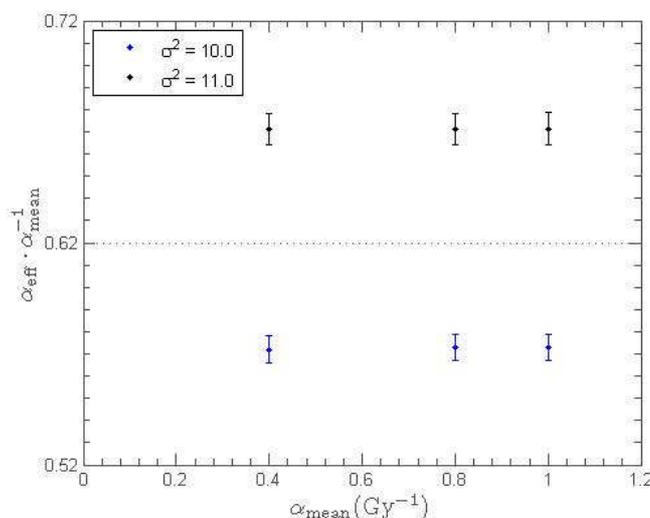
**Figure 1.** Variation of effective radiosensitivity $\alpha_{eff}\cdot(\alpha_{mean})^{-1}$. Error bars indicate the standard error of the mean (SEM).

**Table 1.** TCP $\gamma_{37,mean}$ and $D_{37,mean}$ parameters for uniform dose distribution.

| $\alpha_{mean}$ | $\sigma_x^2 = \sigma_y^2 = 10.0$ | | $\sigma_x^2 = \sigma_y^2 = 11.0$ | |
|---|---|---|---|---|
| | $\gamma_{37,mean} \pm$ SEM | $D_{37,mean} \pm$ SEM | $\gamma_{37,mean} \pm$ SEM | $D_{37,mean} \pm$ SEM |
| 0.4 | 5.436±0.038 | 64.76 ±0.35 | 5.544±0.019 | 61.95±0.23 |
| 0.8 | 5.436±0.038 | 32.38±0.17 | 5.544±0.019 | 30.98±0.11 |
| 1.0 | 5.436±0.038 | 25.90 ±0.14 | 5.543±0.019 | 24.78±0.09 |

**Table 2.** TCP $\gamma_{37,mean}$ and $D_{37,mean}$ parameters for biologically optimum dose distribution.

| $\alpha_{mean}$ | $\sigma_x^2 = \sigma_y^2 = 10.0$ | | $\sigma_x^2 = \sigma_y^2 = 11.0$ | |
|---|---|---|---|---|
| | $\gamma_{37,mean} \pm$ SEM | $D_{37,mean} \pm$ SEM | $\gamma_{37,mean} \pm$ SEM | $D_{37,mean} \pm$ SEM |
| 0.4 | 6.770±0.000 | 47.65±0.03 | 6.771±0.000 | 47.42±0.02 |
| 0.8 | 6.775±0.000 | 23.85±0.01 | 6.775±0.000 | 23.73±0.01 |
| 1.0 | 6.776±0.000 | 19.08±0.01 | 6.776±0.000 | 19.01±0.01 |

**References**
[1]    Ling C, Humm J, Larson S, Amols H, Fuks Z, Leibel S and Koutcher J 2000 *Int. J. Radiat. Oncol. Biol. Phys.* **47** 551
[2]    Bentzen S 2005 *Lancet Oncol.* **6** 112
[3]    Journal of the ICRU Report 83, Vol 10 2010 *Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT)* (Oxford: Oxford University Press)
[4]    Brahme A and Agren A 1987 *Acta. Oncol.* **26** 377
[5]    Webb S and Nahum A 1993 *Phys. Med. Biol.* **38** 653
[6]    Ebert M and Hoban P 1996 *Phys. Med. Biol.* **41** 2125
[7]    Li *et al.* 2012 *Med. Phys.* **39** 1386
[8]    Munro T and Gilbert C 1961 *Br. J. Radiol.* **34** 246
[9]    Bentzen S and Tucker S 1997 *Int. J. Radiat. Biol.* **71** 531
[10]   Wigg D 2001 *Applied radiobiology and bioeffect planning.* (Madison:Medical Physics Publishing) p 236 - 238
[11]   Gregoire V, Jeraj R, Aldo Lee J and O'Sullivan B 2012 *Lancet Oncol.* **13** e292
[12]   Schultheiss T, Zagars G and Peters L 1987 *Radiother. Oncol.* **9** 241

[13]   Suit H, Skates S, Taghian A, Okunieff P and Efird T 1992 *Radiother. Oncol.* **25** 251
[14]   Yang Y and Xing L 2005 *Med. Phys.* **32** 1473