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Technical note

Modelling the effect of spread in radiosensitivity parameters and repopulation rate on the probability of tumour control

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ABSTRACT

Purpose: To investigate the impact of a variable inter-individual spread in the tumour cell radiosensitivity and repopulation rate on the tumour control probability (TCP).
Methods: The radiosensitivity parameters and the repopulation rate are presumed to be log-normally distributed among the population. Corresponding distributions of TCP across the population are built using a Monte-Carlo simulation algorithm. An analytical formula for the TCP distribution is derived for the case of variability in radiosensitivity only and found to be in excellent agreement with the corresponding Monte-Carlo simulations.
Results and Conclusions: It is found that a large variation in individual-patient radiosensitivity results in a dichotomous TCP distribution over the population. In general, the form and width of the TCP distribution depend on the variation in the radiosensitivity. Accounting for tumour repopulation and its variability leads to lower TCP values as expected. It is shown that for a standard fractionation regimen resulting in a population TCP of almost zero, a simple change of the regimen to a hypofractionated one (i.e. typical of SBRT), a decrease in the physical dose is possible such that a beneficial tumour treatment outcome can be still achieved. The reduction in dose will in turn reduce eventual adverse effects caused in the surrounding healthy tissues. This theoretical finding is supported by the increasing amount of clinical evidence for the efficacy of SBRT. The desirability of a pre-clinical independent estimation of the individual radiosensitivity is emphasised.

1. Introduction

The introduction of the mathematical concept of tumour control probability (TCP) by Munro and Gilbert [1] gave rise to a new field of research, namely 'macro radiobiology'. It took several decades for this concept to become well-established together with the resulting clinical implications. Out of 'macro radiobiology' population TCP models were developed [2–4]. These models aim to predict the *observable* quantity, namely the population TCP as a function of dose (and number of fractions). The population TCP models estimate the average response of different individuals over in a population i.e. for what fraction of patients is local tumour control achieved. Considerable efforts have been made to obtain a closed-form expression for the population TCP model based on Poisson statistics [5–8], with the purpose of estimating the most important model parameters from clinical data. In these papers a normal (Gaussian) spread of the individual parameter values over the population is assumed. These efforts have revealed the problem of parameter interrelation and led finally to the work of Carlone et al. [7], where it was shown that D_{50} and γ_{50} (the geometrical parameters of the TCP curve) are the two independent parameters of the TCP population model. D_{50} and γ_{50} respectively are determined by the population parameters, i.e. the mean radiosensitivity, the mean repopulation rate and their standard deviations among a population.

Although individual TCP models are well established, due to the binary nature of the dose-response, an individual TCP cannot be estimated based on clinical data. The individual TCP is a clinically unobservable quantity. It is investigated only theoretically and experimentally in animal experiments with identical animals and cellular

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experiments with identical cellular colonies. However, we are not aware of the existence of attempts to construct and investigate distributions of the individual TCPs in a patient population.

Here we present a numerical and an analytical investigation of the form of the resulting distribution of the *individual* TCPs, for a given population, characterized by the population mean values of the radiosensitivity parameters α,β of the linear-quadratic (LQ) model of cell killing and their standard deviations, as well as the corresponding mean and standard deviation of the repopulation rate. This is done for different radiation regimens and different mean values and standard deviations of the individual model parameters.

2. Methods

The effect of the spread in the radiosensitivity parameters and the repopulation rate on the probability of tumour control is investigated analytically and via Monte-Carlo simulations.

The individual TCP based on the Poisson approximation and accounting for clonogen repopulation is given by [9–14]:

$$TCP = e^{-N_0 e^{-\alpha D-\beta D d+\lambda T}} \tag{1}$$

where N_o is the initial number of tumour clonogens, α and β are the cell radiosensitivity parameters of the LQ model of cell damage, $D = nd$ is the total dose delivered homogeneously to the tumour, d is the dose per fraction, n is the number of fractions, λ is the repopulation rate and T is the total treatment time.

The impact of the variation in the different model parameters on the TCP distribution is studied for two different fractionation regimens delivering equal total dose of 60 Gy – a standard fractionation regime ($d = 2$ Gy, $n = 30$) and a hypofractionated one ($d = 12$ Gy, $n = 5$). Another hypofractionated schedule delivering a lower dose per fraction of 8.5 Gy in 5 fractions resulting in total dose D of 42.5 Gy is also studied. T(n) was calculated numerically according to the standard clinical schedule Mon-Fri. Thus, $T = 39$ days for n = 30 fractions and $T = 4$ days for the hypofractionated schedule (n = 5).

2.1. The case of variation in α only

In this case the term describing the repopulation is ignored. Since parameter α may take only non-negative values we assume that it is log-normally distributed [15]. Hence, a set of random numbers $\{\alpha_i\}$ is constructed using a random number generator subject to a log-normal distribution:

$$dP(\alpha) = f(\alpha)d\alpha = \frac{1}{\sqrt{2\pi}\sigma_{\ln\alpha}}\frac{1}{\alpha}e^{-\frac{(\ln\alpha-\ln\bar{\alpha})^2}{2\sigma^2_{\ln\alpha}}}d\alpha \tag{2}$$

where $dP(\alpha)$ and $f(\alpha)$ are the differential probability and the probability density of α, correspondingly. The mean, $\ln\bar{\alpha}$, and the standard deviation, $\sigma^2_{\ln\alpha}$, of $\ln\alpha$ are related to the mean and standard deviation of α through the following well known relationships [15–17]:

$\bar{\alpha} = e^{\ln\bar{\alpha}+\sigma^2_{\ln\alpha}/2}$ and $\sigma^2_\alpha = e^{2\ln\bar{\alpha}+\sigma^2_{\ln\alpha}}(e^{\sigma^2_{\ln\alpha}}-1)$.

Parameter β is presumed linearly related to parameter α through a fixed α/β ratio, so that

$$\beta_i = const\alpha_i = (\alpha/\beta)^{-1}\alpha_i. \tag{3}$$

Substituting the generated set $\{\alpha_i\}$ and the corresponding set $\{\beta_i\}$ calculated according to Eq. (3) in Eq. (1) for $\lambda = 0$ one gets a set of individual TCP values, $\{TCP_i\}$:

$$TCP_i = e^{-N_0 e^{-\alpha_i D[1+(\alpha/\beta)^{-1}d]}} \tag{4}$$

from which a probability distribution of the individual TCPs can be built representing the spread in the individual tumour control probabilities among the population.

For the case when only α varies over the population and the individual βs are given by Eq. (3), an analytical formula describing the TCP distribution can also be derived based on the relationship [18]:

$$dP(TCP) = f(TCP)dTCP = dP(\alpha) = f(\alpha)d\alpha,$$

where $dP(TCP)$ is the differential probability and $f(TCP)$ is the probability density of TCP accordingly.

It follows (see the Appendix) that the probability density of TCP, $f(TCP)$ is:

$$f(TCP) = \frac{1}{TCP(\ln TCP)}\frac{1}{\ln((-\ln TCP)/N_o)}\frac{e^{-\frac{\left(\ln\left[\frac{-\ln\left(\frac{-\ln TCP}{N_o}\right)}{\widetilde{D}}\right]-\ln\bar{\alpha}\right)^2}{2\sigma^2_{\ln\alpha}}}}{\sqrt{2\pi}\sigma_{\ln\alpha}} \tag{5}$$

where $\widetilde{D} = D + \frac{Dd}{\alpha/\beta}$

2.2. The case of variation in both α and λ

Parameter β is considered again a linear function of α given by Eq. (3) as in *2.1*. The individual TCP values are given then by

$$TCP_i = e^{-N_0 e^{-\alpha_i D[1+(\alpha/\beta)^{-1}d]+\lambda_i T}} \tag{6}$$

Both α and λ are considered to be log-normally distributed (λ also is a parameter which has only non-negative values) each characterized by its mean and standard deviation. Using the same procedure as in *2.1* a set of numbers $\{\alpha_i\}$ are randomly generated. For each α_i, a random number λ_i is generated in the same way. Then for each pair of numbers $\{\alpha_i, \lambda_i\}$ an individual TCP value is calculated according to Eq. (6).

The procedure is repeated N times, where N is 100 000. On the basis of the set of N individual TCP values thereby obtained, $\{TCP_i\}$, a TCP probability distribution is constructed. The Monte-Carlo generated TCP probability distributions are constructed by dividing the TCP interval [0,1] into n ($n = 33$) small ΔTCPintervals and summing the cases of TCP_i values within each ΔTCP interval. Each sum is then divided by N. In the simpler case of variation in α only, each TCP probability value obtained as described above is compared to the product of the analytically calculated TCP probability density (Eq. (5)) and the chosenΔTCPinterval.

3. Results

Four different TCP distributions calculated for the case described in subsection 2.1 (assuming variation in α only) are shown in Fig. 1.

A wide range of the spread in α is considered, represented by four different standard deviations –$\sigma_\alpha = \{0.09; 0.02; 0.01; 0.005\}$ Gy^{-1}. The values of the other parameters are $\bar{\alpha} = 0.26$ Gy^{-1}, $\alpha/\beta = 10$ Gy, $N_o = 10^8$ [19]. The highest value of $\sigma_\alpha = 0.09$ Gy^{-1} was considered in the work of Nahum and Hill [19]. A similar value of σ_α ($\sigma_\alpha = 0.07$ Gy^{-1}) was reported in [20–22].

The calculations are carried out for a fractionation regimen generally accepted as standard in the clinics, namely for $n = 30$ and $d = 2$ Gy. The black dots represent values based on Eq. (5), demonstrating excellent agreement with the Monte-Carlo simulated distributions. It can be seen that although resulting in similar values for the population mean TCP, the distributions are very different. Also for the cases of large σ_α they are considerably different in shape from a normal distribution. This is most clearly demonstrated in the case of $\sigma_\alpha = 0.09$ Gy^{-1} shown in Fig. 1a) where the distribution exhibits a dichotomos behaviour. TCP as a function of α for the chosen fractionation regime is shown in Fig. 2.

Two TCP distributions are shown in Fig. 3 calculated for the case described in subsection 2.2. In both examined cases the values of the mean and standard deviation of the repopulation rate are $\bar{\lambda} = 0.06$ d^{-1} and $\sigma_\lambda = 0.02$ d^{-1}. The variation in λ is combined with a variation in α characterized with the largest σ_α ($\sigma_\alpha = 0.09$ Gy^{-1}) (shown in subplot a)) and with the smallest σ_α ($\sigma_\alpha = 0.005$ Gy^{-1}) (shown in subplot b)) examined in Fig. 1. The rest of the parameter values as well

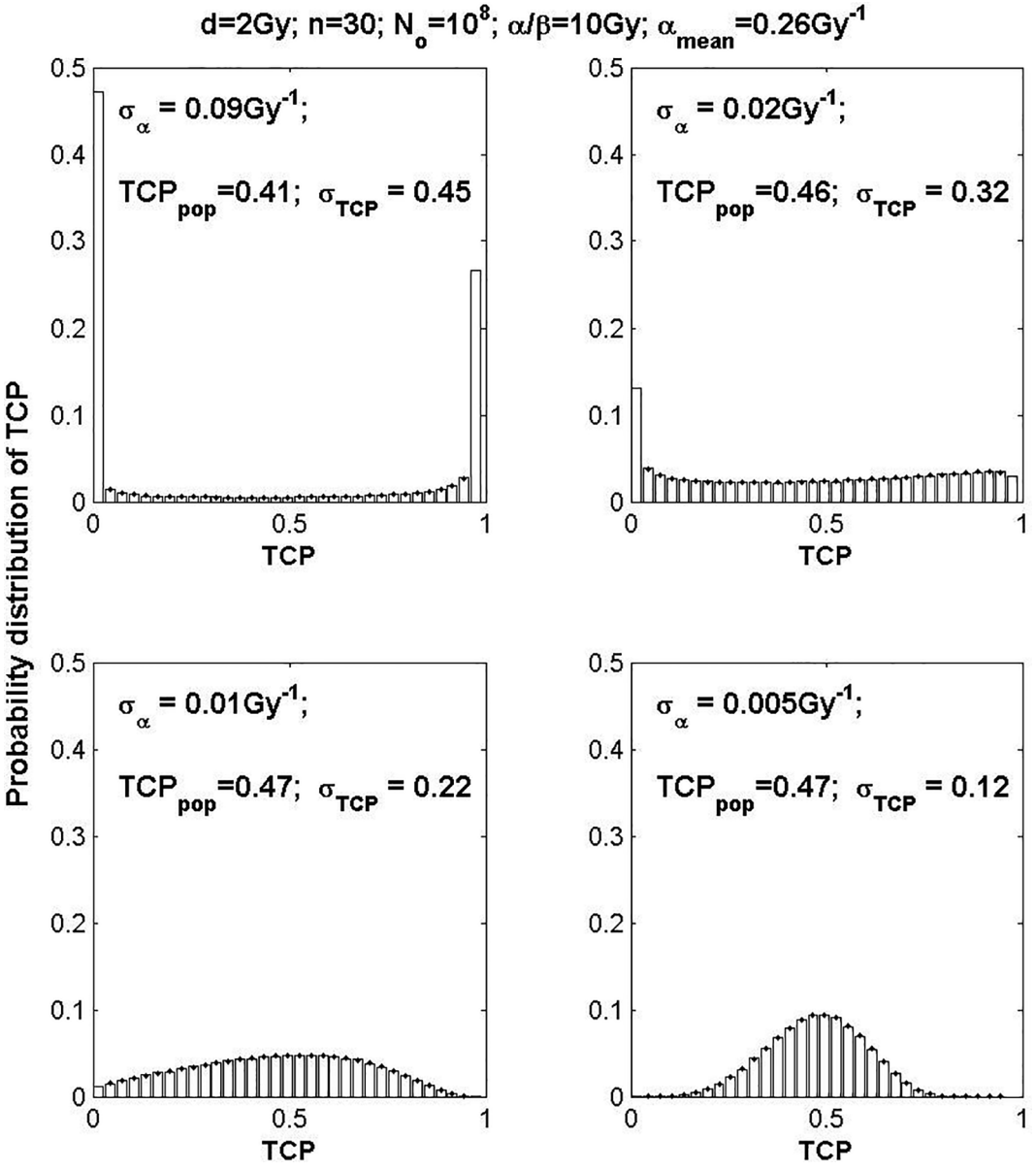

Fig. 1. TCP distributions for the case of spread in α only, calculated via a Monte Carlo simulation – columns and analytically according to Eq. (5) – dots. Four different standard deviations of α are used – $\sigma_\alpha = 0.09\,\mathrm{Gy}^{-1}$, shown in Fig. 1a); $\sigma_\alpha = 0.02\,\mathrm{Gy}^{-1}$ – Fig. 1b); $\sigma_\alpha = 0.01\,\mathrm{Gy}^{-1}$ – Fig. 1c); $\sigma_\alpha = 0.005\,\mathrm{Gy}^{-1}$ – Fig. 1d). The rest of the parameter values are $\bar{\alpha} = 0.26\,\mathrm{Gy}^{-1}$, $\alpha/\beta = 10$ Gy, $N_o = 10^8$. The calculations are carried out for a standard fractionation regime – $d = 2$ Gy; $n = 30$.

as the fractionation regimen are the same as in Fig. 1. The TCP distributions from Fig. 1a) and d) are also shown in *black* for comparison. It can be seen that the inclusion of repopulation, not surprisingly, considerably worsens the expected treatment outcome.

Different values for the initial number of cells, the mean radiosensitivity and the mean repopulation rate are chosen for the calculation of the TCP distributions shown in Fig. 4 ($N_o = 10^4$, $\bar{\alpha} = 0.16\,\mathrm{Gy}^{-1}$, $\bar{\lambda} = 0.19\,\mathrm{d}^{-1}$). These values are chosen equal to the best-fit values of the same parameters obtained in Reference [23] through fitting an individual TCP function to animal data obtained in an experiment by Fisher and Moulder [24]. These values are considered to characterize the most resistant cellular sub-population of the tumour, which determines the tumour dose–response in terms of TCP.

Two TCP distributions are shown in Fig. 4a) calculated for the standard fractionation regimen and the α/β ratio used so far ($n = 30$ and $d = 2$ Gy; $\alpha/\beta = 10$ Gy) – one corresponding to variability in α only as described in subsection 2.1, shown in *black* and one considering also the effect of repopulation and the variability in the repopulation rate (subsection 2.2) shown in *white*. σ_α and σ_λ have the same values as in Fig. 3b). It can be seen that the presence of repopulation *drastically* decreases the expected TCP, to an extent that the predicted TCP for *all* patients becomes practically zero.

The same two TCP distributions are calculated in this case for a hypo-fractionated regimen ($n = 5$ and $d = 12$ Gy) with the same total

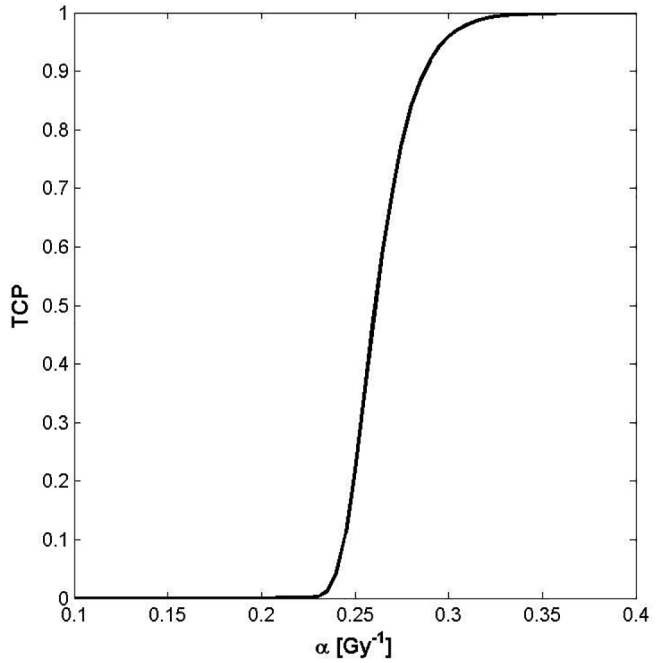

Fig. 2. A graph of TCP as a function of α for $\alpha/\beta = 10$ Gy, $N_o = 10^8$ and $d = 2$ Gy; $n = 30$.

dose of 60 Gy for the same parameter values as in Fig. 4a). The two distributions coincide both predicting a population TCP of one with practically zero variation. This imperative result indicated that perhaps 60 Gy was an unnecessarily high physical dose and prompted the search for a minimal dose per fraction and hence minimal total physical dose, which will still result in high enough population mean TCPs with low variations, i.e. narrow distributions. In Fig. 4b) are shown such distributions corresponding to $d = 8.5$ Gy and $D = 42.5$ Gy.

The corresponding BED values calculated for the assumed α/β ratio of 10 Gy are 72 Gy for the standard regimen, 132 Gy for the hypofractionated one with $d = 12$ Gy and 78.6 Gy for the hypofractionated one with $d = 8.5$ Gy.

Although the main goal of this work is investigating the effect of spread in radiosensitivity parameters and repopulation rate on TCP, the effect on the normal tissue of the different fractionated regimens should also be considered. For example SBRT schedule delivering to the prostate approximately 40 Gy in 5 fractions was studied in paper [25] – a regimen quite similar to the one considered in Fig. 4b). The estimated NTCP, based on Lyman's model (see Table 1 from Ref. [25] with $\alpha/\beta = 3$ for rectum) was less than 1% for rectum and was much lower, i.e. almost zero for bladder. For the case of 60 Gy delivered to the tumour in 30 fractions the corresponding DVHs for rectum and bladder were recalculated and the corresponding NTCPs were found to be even lower. In the case when 60 Gy are delivered to the tumour in 5 fractions the NTCP of bladder remains almost negligible. Unfortunately for rectum it becomes unacceptably high – NTCP ~ 20–30%.

The diversity of the different theoretically obtained TCP distributions poses the question of their impact on the observable quantity, i.e. the population mean TCP and its variation. In order to check whether it is possible to reconstruct the inherent TCP distribution via post-treatment analysis, the following pseudo-experiment was carried out for the dichotomic TCP distribution shown in Fig. 1a). This distribution is chosen since it is most extremely different from a normal distribution. A group of (30) 'patients' was sampled such that an individual TCP value, TCP_i, was assigned to each 'patient' via a random number generator subject to the distribution given with Eq. (5) for $\bar{TCP} = TCP_{pop} = 0.41$, $\sigma_{TCP} = 0.45$. Then, using a random number generator of numbers uniformly distributed between zero and one, another random number, l_i, is generated for each 'patient'. It is compared to the individual TCP_i previously assigned to this 'patient' and if $l_i \leq TCP_i$ a case of tumour cure is subsequently recorded. The number of tumour cures is then summed. This procedure is repeated a large number of times (200 000) and a number of cures for each group of 30 'patients is recorded. A distribution is subsequently built of the obtained numbers of cures shown as a histogram in Fig. 5. A distribution is also built of the number of successes subject to the binomial distribution of order $m = 30$ with a probability of success $p = 0.41$, shown with a solid line in Fig. 5. It can be seen that both distributions match perfectly. Thus it is demonstrated that the only observable in the clinics quantity, the number of cures in a group of patients, can provide information only on the mean TCP of the group. Eventually a distribution of the possible number of cures in a group (mean TCP values) can be built if many groups are treated. The inherent distribution of the individual TCPs cannot be reconstructed via a post-clinical analysis.

4. Discussion

The rather unexpected form of the TCP distribution shown in Fig. 1a) is due to the steepness of the individual TCP as a function of α (as can be seen from Fig. 2) and the chosen large value of σ_α. The mean value of α is chosen to correspond to a TCP value around 0.5. The high value of σ_α results in the formation of two rather large sub-groups of individuals with low and high radiosensitivities, such that the corresponding TCP values are zero and one. That is, the patients in one of the groups will be *deterministically* cured, while the patients in the other group will fail to respond to the treatment altogether. Populations with lower σ_α value will consist of individuals most of whom will have intermediate chance of being cured. Since the population average TCP value is almost the same for the different populations, characterized by different σ_α values (as shown in the Results section), a simple post-treatment statistical analysis will not be able to differentiate between the different cases. Indeed, as can be seen from Fig. 5 the observable outcome, i.e. the distribution of the number of successes among different randomly chosen sub-groups is solely determined by the mean TCP value for the whole group of patients. However, while in the latter case (small σ_α) all patients will have some chance of being cured, in the first case (large σ_α) there is a group, which is unfortunately predestinated to fail.

The inclusion of the repopulation in the analysis naturally leads to deterioration in the expected treatment outcome measured in terms of inherent individual TCPs. The impact of repopulation is especially drastic for high values of the repopulation rate, i.e. for aggressive types of tumours, as shown in Fig. 4a) where a very high mean TCP value ($TCP_{mean} = 0.9$) falls to practically zero after considering tumour repopulation thus rendering the treatment completely ineffective for the whole population.

It is shown however, that with a change in the fractionation regimen to a hypofractionated one without increasing the total dose delivered to the tumour a huge improvement in the expected outcome can be achieved. It is demonstrated in Fig. 4b) that a decrease in the physical dose is possible such that a beneficial tumour treatment outcome can be still achieved. The reduction in dose will in turn reduce eventual

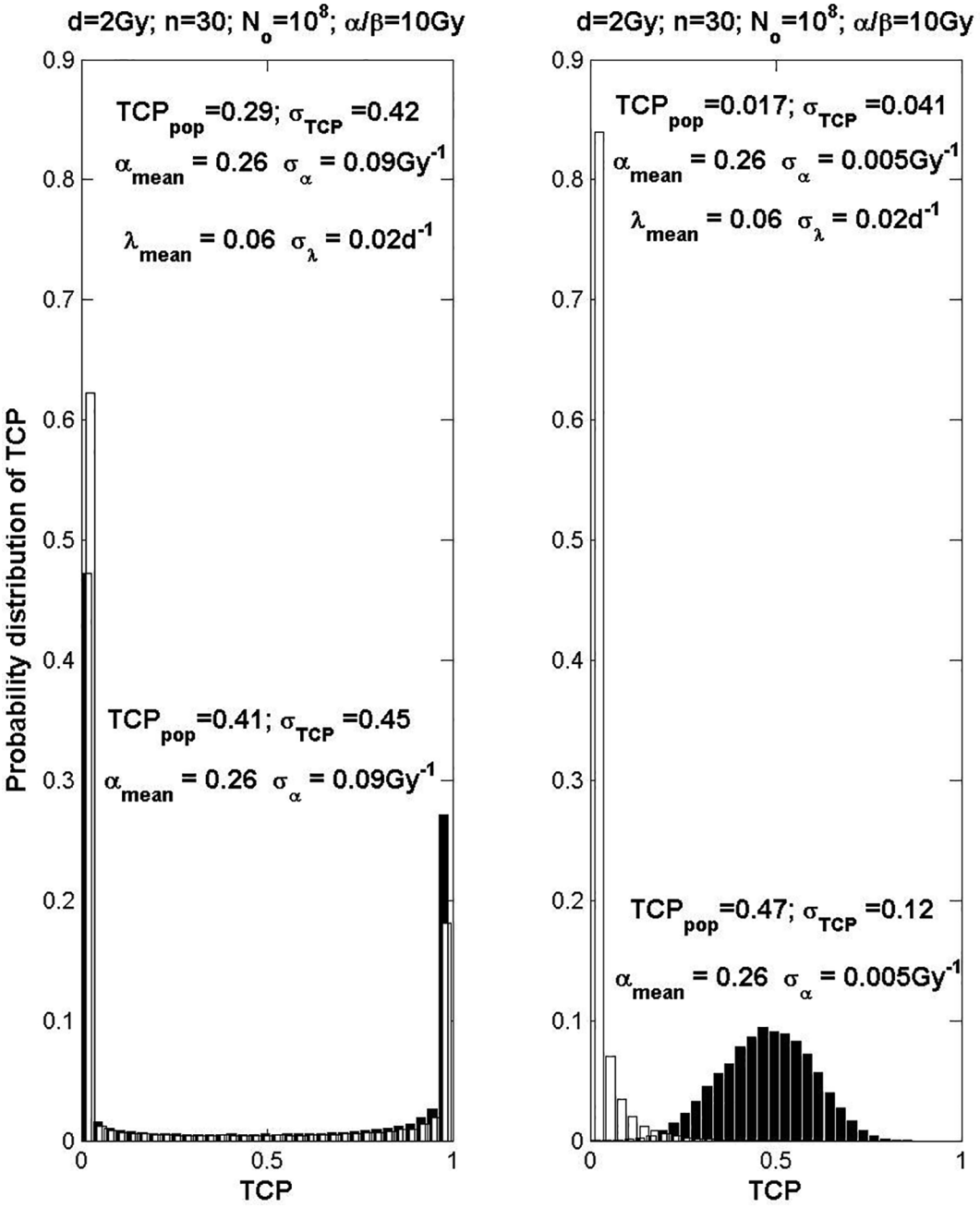

Fig. 3. TCP distributions accounting for repopulation and variations in both α and λ – bars in white. The repopulation rate is characterized by its population mean value $\bar{\lambda} = 0.06\ d^{-1}$ and standard deviation $\sigma_\lambda = 0.02\ d^{-1}$. It is combined with the cases of the highest spread in α – $\sigma_\alpha = 0.09\ Gy^{-1}$ – Fig. 3a) and the lowest one – $\sigma_\alpha = 0.005\ Gy^{-1}$ – Fig. 3b) as used in Fig. 1. The rest of the parameter values and the fractionation regime are the same as in Fig. 1. The corresponding TCP distributions, calculated for spread in α only (shown in Fig. 1a) and d)) are given for comparison – bars in black.

adverse effects caused in the surrounding healthy tissues.

This result is a clear demonstration of the superiority of the hypo-fractionated treatments compared to the standard ones. This theoretical result is also supported by the increasing amount of clinical evidence for the efficacy of SBRT.

In a recent research [26] on high dose-rate brachytherapy dose-response (which could be considered in this case similar to the external fractionated radiotherapy) we reported 3 cases of failed tumour control out of approximately 80 patients. The comparison of the dose-volume histograms in these three cases with the averaged one has shown that the patients exhibiting a local control failure have received even higher doses than average. This result is in accordance with the study presented here since it demonstrates the existence of a subgroup of patients with apparently very high radio-resistance compared to the rest of the

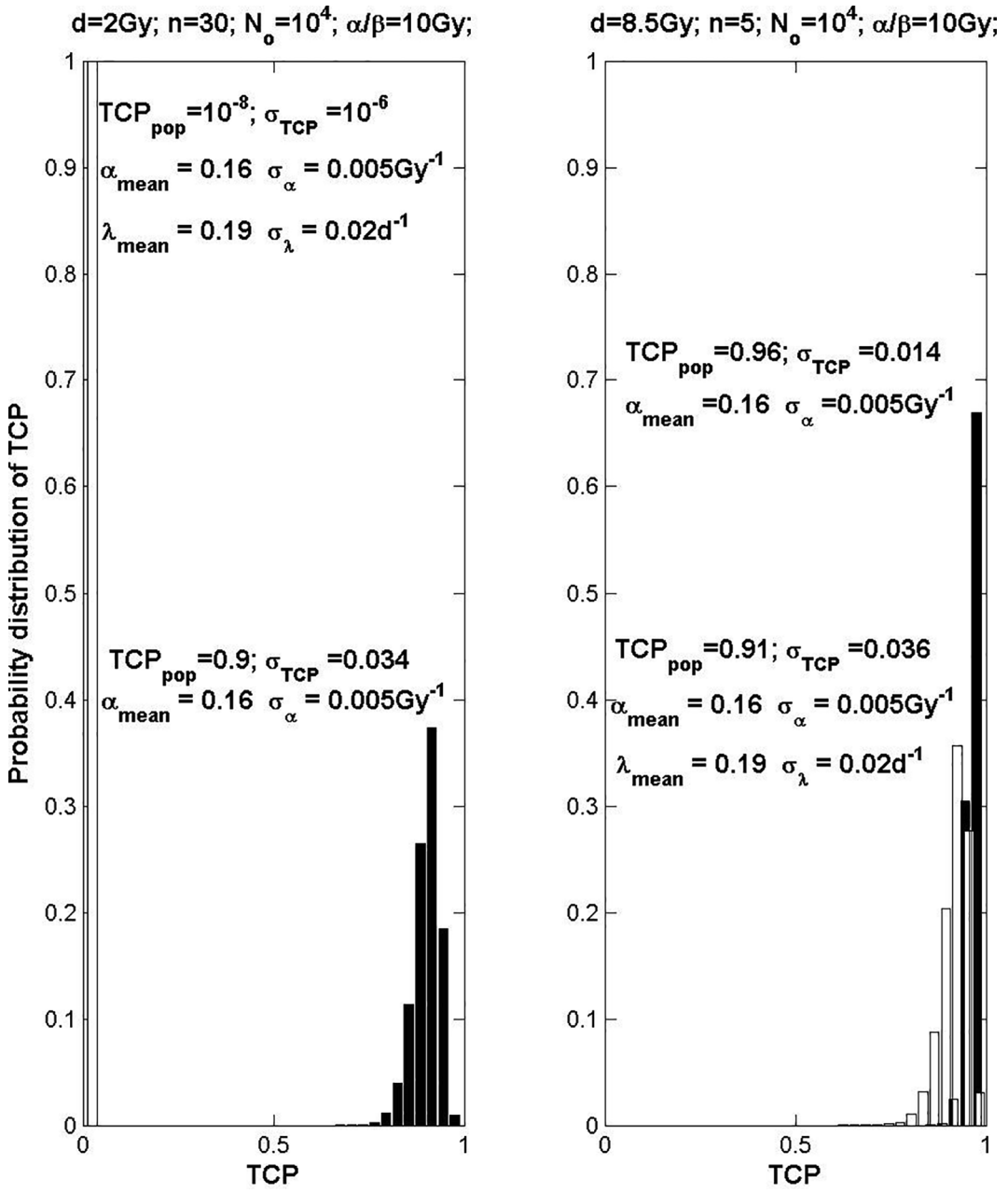

Fig. 4. TCP distributions calculated for a different set of TCP parameter values – $N_o = 10^4$; $\bar{\alpha} = 0.16$ Gy^{-1}; $\sigma_\alpha = 0.005$ Gy^{-1}; $\alpha/\beta = 10$ Gy; $\bar{\lambda} = 0.19$ d^{-1}; $\sigma_\lambda = 0.02$ d^{-1}. In Fig. 4a) are shown TCP distributions calculated for the standard fractionation regimen ($d = 2$ Gy; $n = 30$) – columns in white for variation in both α and λ and columns in black for variation in α only. In Fig. 4b) are shown TCP distributions calculated for a hypo-fractionation regimen ($d = 8.5$ Gy; $n = 5$) – columns in white for variation in both α and λ and columns in black for variation in α only.

group. It also stresses the necessity of independent estimation of the individual radiosensitivity.

5. Conclusion

Using Monte Carlo methodology we have built distributions of the individual TCPs for different populations characterized by certain population parameter values.

The following propositions are supported by the presented theoretical investigation:

- Since there may be cases for which the prescribed treatment will inevitably lead to failure of local tumour control for some of the patients, it is important to develop and employ independent methods of estimating the cellular radiosensitivities of the individual patients, to pre-identify such radioresistant patients, and to

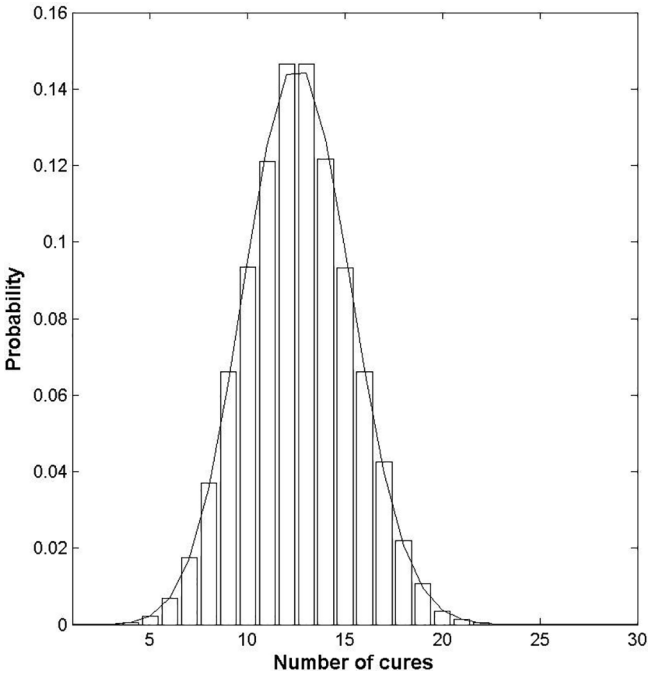

Fig. 5. Distribution of the "observed" number of cures constructed based on the dichotomic TCP distribution of Fig. 1a) compared to the binomial distribution of order m = 30 of the number of successes with probability of success equal to the mean TCP value from Fig. 1a).

offer them treatment with an alternative total dose/number of fractions (provided that the NTCP is acceptable) such that the predicted TCP is sufficiently high. Alternatively

- A database may be created of pre-clinical estimates of the radiosensitivities of a representative sample of patients which will give information on the possible range of radiosensitivity values for a given tumour type in a population. Thus a distribution of the individual radiosensitivities for this tumour type can be constructed. On its bases expected individual TCPs can be calculated and their distribution can be built for different treatment regimens. And a search for an optimal regimen resulting in a narrow TCP distribution with high population mean can be performed so that a high tumour control probability can be achieved for the *whole* population.
- If no pre-clinical information is available on possible individual radiosensitivity parameters hypo-fractionated regimens or, in general, regimens which result in very high individual and hence population TCP values, even for adverse parameter values, (i.e. low mean radiosensitivity and high mean repopulation rate such as the ones used in Fig. 4) may be applied (provided that the NTCP is acceptable).

Appendix

From $P(TCP) = f(TCP)dTCP = P(\alpha) = f(\alpha)d\alpha$ follows:

$$f(TCP) = f(\alpha)\frac{d\alpha}{dTCP} \tag{A1}$$

We can rewrite the TCP expression given with Eq. (4) in the form

$$TCP = e^{-N_0 e^{-\alpha\widetilde{D}}} \quad \text{where} \quad \widetilde{D} = D + \frac{Dd}{\alpha/\beta}$$

It can be solved for α giving: $\alpha = \frac{-\ln\left(\frac{-\ln TCP}{N_0}\right)}{\widetilde{D}}$ wherefrom

$$\frac{d\alpha}{dTCP} = \frac{-1}{\widetilde{D}TCP\ln TCP} \tag{A2}$$

We can rewrite $f(\alpha)$ from Eq. (2) in terms of TCP:

$$f(\alpha) = \frac{1}{\sqrt{2\pi}\sigma_{\ln\alpha}}\frac{\widetilde{D}}{-\ln((-\ln TCP)/N_0)}e^{-\frac{\left(\ln\left[\frac{-\ln\left(\frac{-\ln TCP}{N_0}\right)}{\widetilde{D}}\right]-\ln\bar{\alpha}\right)^2}{2\sigma^2_{\ln\alpha}}} \tag{A3}$$

Substituting (A2) and (A3) in (A1) one gets:

$$f(TCP) = \frac{1}{TCP(\ln TCP)}\frac{1}{\ln((-\ln TCP)/N_0)}\frac{e^{-\frac{\left(\ln\left[\frac{-\ln}{\widetilde{D}}\left(\frac{-\ln TCP}{N_0}\right)\right]-\ln\bar{\alpha}\right)^2}{2\sigma^2_{\ln\alpha}}}}{\sqrt{2\pi}\sigma_{\ln\alpha}}$$

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