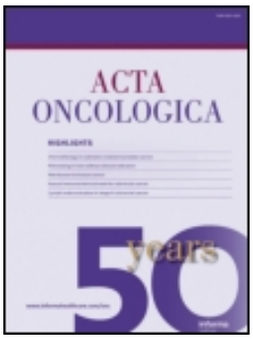

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ORIGINAL ARTICLE

Dose-effect models for risk – relationship to cell survival parameters

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Abstract
There is an increased interest in estimating the induction of cancers following radiotherapy as the patients have nowadays a much longer life expectancy following the treatment. Clinical investigations have shown that the dose response relationship for cancer induction following radiotherapy has either of two main characteristics: an increase of the risk with dose to a maximum effect followed by a decrease or an increase followed by a levelling-off of the risk. While these behaviours have been described qualitatively, there is no mathematical model that can explain both of them on mechanistic terms. This paper investigates the relationship between the shape of the dose-effect curve and the cell survival parameters of a single risk model. Dose response relationships were described with a competition model which takes into account the probability to induce DNA mutations and the probability of cell survival after irradiation. The shape of the curves was analysed in relation to the parameters that have been used to obtain them. It was found that the two main appearances of clinical data for the induction of secondary cancer following radiotherapy could be the manifestations of the particular sets of parameters that describe the induction of mutations and cell kill for fractionated irradiations. Thus, the levelling off appearance of the dose response curve could be either a sign of moderate to high inducible repair effect in cell survival (but weak for DNA mutations) or the effect of heterogeneity, or both. The bell-shaped appearance encompasses all the other cases. The results also stress the importance of taking into account the details of the clinical delivery of dose in radiotherapy, mainly the fractionated character, as the findings of our study did not appear for single dose models. The results thus indicate that the shapes of clinically observed dose response curves for the induction of secondary cancers can be described by using one single competition model. It was also found that data for cancer induction may be linked to *in vivo* cell survival parameters that may be used for other modelling applications.

The increased success of radiotherapy (alone or in combination with other forms of treatment) has led to an increase in the life expectancy for many patients and especially for children who may live for decades after treatment. This success is achieved through advanced treatment techniques such as intensity modulated radiation therapy (IMRT) and conformal radiotherapy techniques (CRT) which result in quite different patterns of irradiation of the healthy tissues. Thus, IMRT causes relatively large volumes of healthy tissues to be irradiated with low doses of radiation, while the conformation of the dose to the target in CRT means that only small volumes of tissue surrounding the clinical target volume are irradiated but not always with very low doses. As the risks for stochastic effects associated with these techniques may not be the same [1,2] it may therefore be necessary to evaluate the various treatment plans not only from the point of view of the local control and deterministic complications in the normal tissues (as it is largely done today), but also with respect to the stochastic effects which may appear. Indeed there have been several proposals that the risk of cancer induction should be used as further criteria for the ranking of treatment plans along with the estimation of the deterministic effects [3–8]. This however requires the use of reliable models and accurate parameters which may not always be extracted from the experimental studies.

Most models put forward for this purpose are based on the competition between cell survival and induction of DNA mutations which has been suggested a long time ago [9–11]. The traditional expectation of the competition is a bell-shaped curve reflecting an increase of the risk with dose to a maximum effect followed by a decrease as for higher doses the obviously rising incidence with dose is counteracted by the falling number of surviving cells

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which eventually appears as a falling incidence of the effect.

Studies of cancer induction after radiotherapy have however shown that the process can generally be described as having either of two main characteristics. Thus, it has been observed that the dose effect curve may have a bell shape with a maximum in a narrow dose window [4,12], or alternatively, the dose effect curve might increase at low doses and then level-off at least for a relatively broad range of doses [13]. Both these behaviours have been described mainly qualitatively, but to the best of our knowledge no mathematical model has been put forward to explain both appearances on mechanistic grounds.

Generally it has been suggested that the plateau behaviour is the result of increased cell survival, but in the light of the competition between cell kill and induction of DNA mutations, a higher cell survival would only mean that the incidence will continue to rise with dose and that the peak in effect will be reached at higher doses. Therefore, other reasons could be put forward for the shape of the risk curve. Among them one could count the hyperradiosensitivity observed at low doses and thought to illustrate the inducibility of the cellular repair mechanisms [14] as well as the heterogeneity specific to large biological datasets. With respect to the latter aspect, it has indeed been shown that taking heterogeneity into account for other radiotherapy applications influences very much the evaluation of clinical data [15].

This paper aims to investigate the above-mentioned aspects of cell survival and induction of DNA mutations as well as particular features of radiation treatment such as fractionation in relation to their influence on the theoretical predictions for the risk of cancer induction. It will also deal with the relationship between the parameters of the cell survival or DNA mutations model and the clinical observations for the appearance of secondary cancers after radiotherapy.

Materials and methods

The theoretical predictions for the risk of cancer following radiotherapy were analysed with a modified version of the UNSCEAR LQ-based model for cancer induction [16] which has previously been successfully used to predict the risk of secondary cancers for several sites [8]. Thus, for fractionated treatments the risk is thought to be given by Equation 1:

$$Effect = \left(\alpha_1 D + \frac{\beta_1 D^2}{n}\right) \times \exp\left[-\left(\alpha_2 D + \frac{\beta_2 D^2}{n}\right)\right] \quad (1)$$

where D is the total dose given in n fractions. It has to be mentioned that the fractionated delivery of radiation is an aspect usually ignored for the estimation of the cancer risk from radiotherapy.

As with the UNSCEAR model [16], the first term of the product in Equation 1 describes the induction of DNA mutations and the second term describes the cell survival. Furthermore, for very low doses the dose-effect relationship can be approximated as being linear with the slope α_1, as the exponential term in Equation 1 is almost unity and the quadratic term in the DNA mutation factor can be neglected. Thus, the model is compatible with the linear risk model valid for low doses and the α_1 parameter may be assumed to be equal to the risk coefficients found in epidemiological studies with low doses or recommended by international committees such as ICRP [17].

Equation 1 can be modified to take into account the inducible repair effect which manifests itself as a region of high radiosensitivity to low doses in the survival response of mammalian cells. Thus, instead of the LQ model [18–20] which has been proven to fail to describe the response of tissues at very low doses, one could use the alternative linear quadratic model with inducible repair (LQ/IR) proposed by Joiner and Johns [21] which takes into consideration the preparedness of the cellular repair mechanisms for dealing with the DNA damage inflicted by radiation (Equation 2).

$$SF(d) = \exp\{-\alpha_R \cdot [1 + (IRR - 1) \cdot e^{-d/D_C}] \cdot d - \beta \cdot d^2\} \quad (2)$$

where d is the radiation dose, α_R and β are the classical LQ parameters, D_C is a parameter describing the efficiency of the activation of repair at low doses and *IRR* or inducible repair ratio is a measure of the total inducibility of the repair mechanism. The D_C parameter was observed to vary little around 0.2 Gy and it has relatively little influence on the general shape of the cell survival curve. *IRR* on the other hand is very important for the shape of the cell survival curve at low doses and it was found to have almost any value between 1 and 20 or even more [14].

The LQ/IR model and the LQ model diverge only in the predictions for effects at low doses (below 1 Gy or even 0.5 Gy). However, bearing in mind that the doses received by the healthy tissues are considerably lower than the therapeutic doses and that these doses are the result of repeated delivery of fractional doses which quite often are below 1 Gy, it seems that inducible repair may indeed play an important role for the induction of cancer.

In order to investigate the influence of parameter heterogeneity, we have assumed that the individual values are log-normally distributed around a central value. For ease of calculation we have further

assumed that the distribution was discrete, each individual value in the distribution having an associated weight w_i, given by the normalised probability distribution function. The resolution of the discrete distribution was fine enough to minimise the differences from using a continuous distribution. The final dose effect curve was then calculated as the weighted average of the dose effect curves corresponding to the individual values in the distribution.

$$Effect = \sum_i w_i \cdot Effect_i \qquad (3)$$

where $Effect_i$ is the corresponding dose effect curve for the parameter having the weight w_i.

Results and discussion

The influence of inducible repair

We have first considered the case when cell survival is described by the inducible repair model (Equation 2), while the induction of DNA mutations is described by the classical LQ equation. Figure 1 shows the risk predictions for fairly resistant tissues ($SF_2 = 70\%$) with different α/β values. The chosen α/β values cover the interval of values that have been observed experimentally in functional assays [22] for most of the tissues at risk in the ICRP Publication 60 [17]. It appears that the risk predictions for most tissue types seem to level off for a large range of total doses if the inducible repair ratio IRR for cell survival is moderate to high (between 3 and 8). The variations from a purely flat response are very small and therefore not likely to be observed in a reasonably sized epidemiological study. It has to be stressed here that the flattening feature appears only for fractionated treatments, the curve for single doses being bell-shaped. This difference is indeed expected as for fractionated treatments the effect is the result of adding many fractional doses with a magnitude in the dose range where the inducible repair process manifests itself.

The results in Figure 1 therefore suggest that the levelling off of the risk for cancer induction might be a manifestation of the inducible repair effect. This feature seems to appear only for tissues with moderate to high α/β values with intrinsic radiosensitivities within a narrow widow around $SF_2 = 70\%$. For the more resistant tissues, the dose effect curve increases continuously as more cells with DNA mutations survive the radiation dose, while for the less resistant tissues, the cell killing quickly overcomes the DNA mutation term and the dose response curve has a maximum effect appearance. It has to be mentioned that it has previously been suggested that the levelling off feature might be a manifestation of particularly high cellular radioresistance [1,2]. Our results however suggest that extremely high cellular radioresistance might not lead to a flattening of the dose response curve. Furthermore, radioresistance by itself might not be enough to explain the shape of the dose response curve and that radioresistance also has to be associated with inducible repair as illustrated in Figure 1.

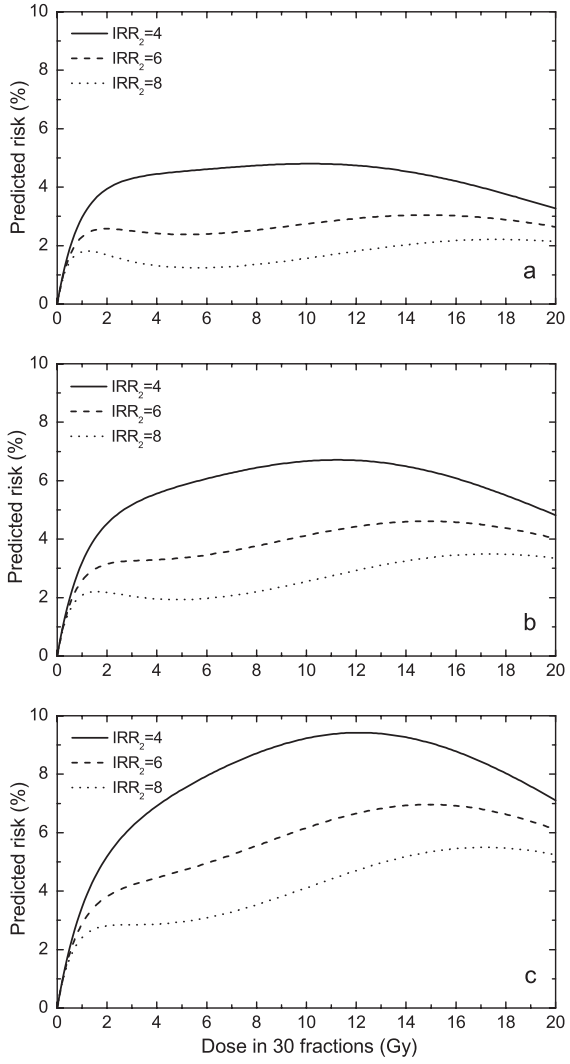

Figure 1. Risk predictions according to the competition model for various assumptions regarding the magnitude of the inducible repair for cellular survival. Upper panel $\alpha/\beta = 10$ Gy; middle panel $\alpha/\beta = 5$ Gy; lower panel $\alpha/\beta = 3$ Gy. ($\alpha_1 = 0.05$ Gy^{-1}, $SF_2 = 70\%$, $IRR_1 = 1$)

While the appearance of the inducible repair for cellular survival has been seen *in vitro* in a wide range of cell lines using single dose experiments [14,23–30] as well as for fractionated experiments *in vivo*, both in animal and in human tissues [21,31–34], comparatively little is known about its appearance for DNA mutations. In fact, quite little data exists for chromosome aberrations at very low doses to give a definitive answer to this question. However,

a study by Gershkevitsh et al. [35] has recently shown data for chromosome aberrations following prostate radiotherapy with fractionated treatments that has an appearance characteristic to the inducible repair effect. This does not appear for all the data sets shown in their study, but given the large variability of biological data it does suggest that inducible repair might appear for chromosome aberrations as well. In fact, as inducible repair is a manifestation of the cellular repair mechanisms for DNA damage [14,36,37], there is no reason why it should appear for cell survival but not for DNA mutations.

In this light we have also considered the case when both the cell survival term and the DNA mutations term are described by the inducible repair model.

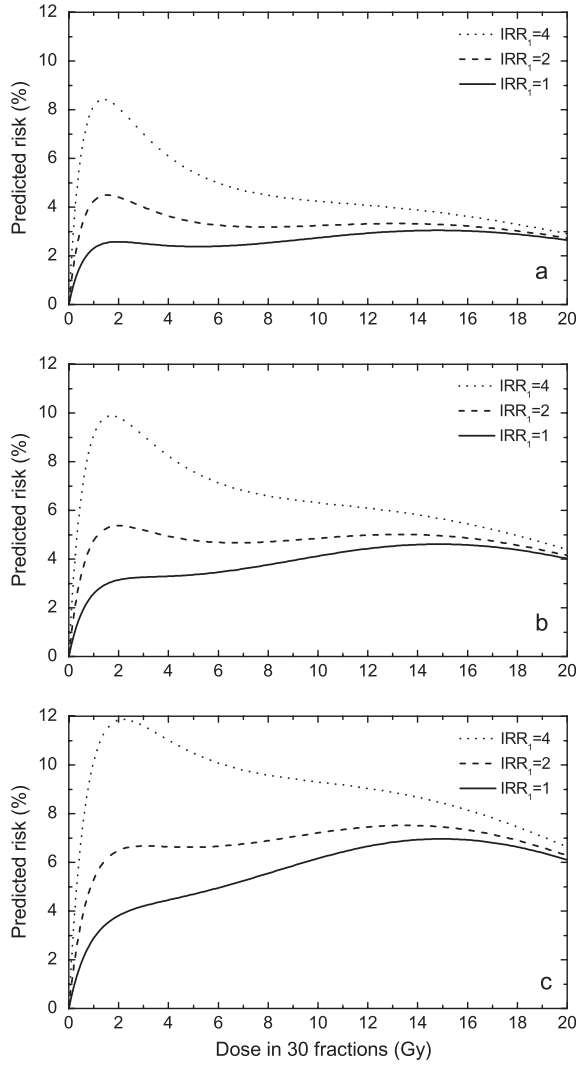

Figure 2. Risk predictions according to the competition model for various assumptions regarding the magnitude of the inducible repair for induction of DNA mutations. Upper panel $\alpha/\beta = 10$ Gy; middle panel $\alpha/\beta = 5$ Gy; lower panel $\alpha/\beta = 3$ Gy. ($\alpha_1 = 0.05$ Gy^{-1}, $SF_2 = 70\%$, $IRR_2 = 6$)

Figure 2 shows that the levelling off feature disappears rapidly if the inducible repair ratio for DNA mutations is larger than 2 or 3 and that the dose effect curve gains a bell-shaped appearance. We have also studied the case when the inducible repair model describes the DNA mutations term, while cellular survival is described by the classical LQ model. However, the dose effect curve in this case only had a bell-shaped appearance (data not shown).

Our results therefore seem to suggest that the levelling off feature may be a manifestation of the inducible repair effect in cell survival. If considerable inducible repair exists for both DNA mutation and cell survival or at least for DNA mutations, the dose effect curve for the risk of cancer induction has a bell-shaped appearance. The same is true if inducible repair is very weak in both terms (classical LQ case). If however cell survival is characterised by moderate inducible repair (IRR between 4 and 6) and DNA mutations by very weak inducible repair, then the dose effect curve has the levelling off appearance.

These findings also suggest that treating radiation induced DNA mutations and radiation induced cell killing as equally radiosensitive may not be correct, even though both are related to DNA damage. It depends on the accident that "radiation induced" is a univocal linguistic coincidence, whereas the two processes might not be simply or directly linked. This is not surprising taking into consideration the fact that cell survival is a manifestation of non-viable repair of DNA damage, while cancer inducing mutations are the result of misrepair of DNA lesions. Thus, it may seem reasonable not to try and relate parameters characterising these two processes.

The influence of parameter heterogeneity

Clinical data on cancer induction from radiotherapy are the result of several thousands (up to hundreds of thousands sometimes) of patients and therefore heterogeneity in the individual radiosensitivity has to be taken into consideration as a possible parameter that may influence the appearance of the dose response curve. The influence of the heterogeneity of intrinsic radiosensitivity is illustrated in Figure 3. Thus it seems that for fairly resistant tissues (distributions centred on $SF_2 = 70\%$), a wide distribution of the parameters (coefficient of variation above 40 – 50%) could result in a flattening of the dose effect curve over a relatively broad dose range. Such widths of the distribution are within the experimental observations, as for example a study of intrinsic radiosensitivities of patient biopsies has yielded coefficients of variation as large as 43% [38]. This study included inter-laboratory variations that lead

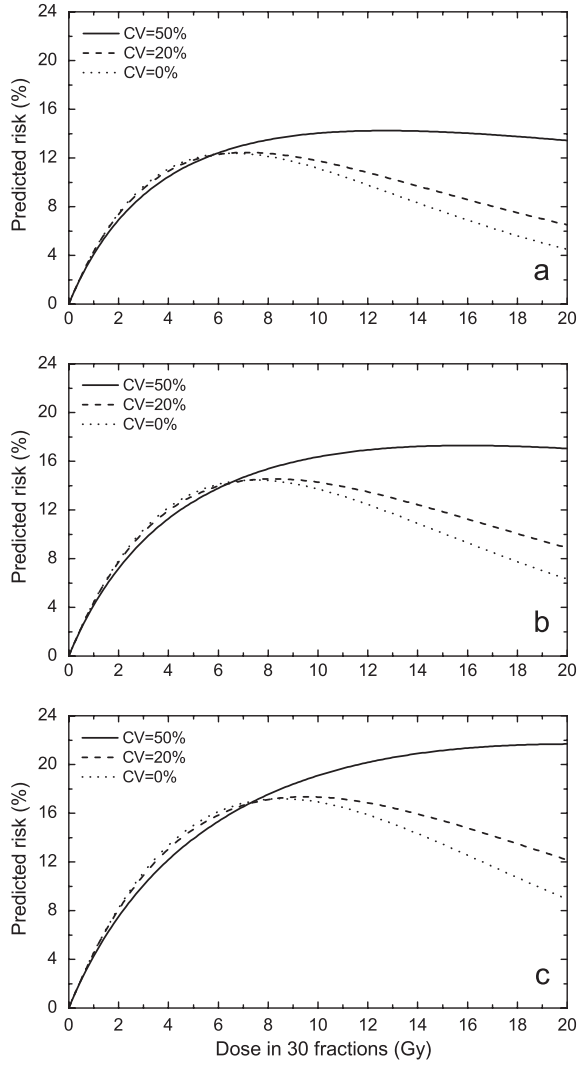

Figure 3. Risk predictions according to the LQ-based competition model for various assumptions regarding the heterogeneity of cellular radiosensitivity. Upper panel $\alpha/\beta = 10$ Gy; middle panel $\alpha/\beta = 5$ Gy; lower panel $\alpha/\beta = 3$ Gy. ($\alpha_1 = 0.05$ Gy^{-1}, $SF_2 = 70\%$).

to a broadening of the distribution of parameters, but they simulate very well the variability of data that might be expected from multi-centre data such as analyses of induction of second cancers. The flattening of the dose response curve also appeared for a combination of inducible repair and heterogeneity in radiosensitivity, but for reduced magnitudes of these two features compared to the case when they were considered individually.

It has to be stressed again that the flattening feature in Figure 3 appears only if the equation for fractionated treatments is used, the curve for single doses having a bell-shaped appearance. It was further found that for distributions of values centred on $SF_2 = 50\%$, the dose effect curve failed to show a levelling-off for reasonable heterogeneity (data not shown), suggesting that the levelling off feature is particular to fairly radioresistant tissues.

The choice of parameters

We have also investigated the relationship between the shape of the dose-response relationship and some other parameters in Equation 1. A first choice was the α/β ratio, as this parameter describes the curvature of the LQ cell survival curve. We have therefore tested the appearance of the dose effect curve given by Equation 1 for a wide range of α/β values while assuming a cell survival compatible with a maximum dose around 4 – 5 Gy, as seen in epidemiological studies [12]. We have however found that the α/β parameter seems to have little influence on the risk curve (Figure 4), this suggesting that the levelling off appearance of some clinical data may not be related to the curvature of the cell survival curve.

It should also be interesting to investigate the relationship between the parameters in Equation 1 and the position of the maximum of the risk curve. The "optimal dose" for which the maximum of the dose effect curve is seen can be found mathematically as the solution of the equation:

$$\frac{d(Effect)}{dD} = 0 \tag{4}$$

where D is the total dose.

For the case when the effect is given by Equation 1, one obtains, after some mathematical manipulation of Equation 4, including the rewriting of the beta parameters of the LQ model as a function of the alpha and (α/β) parameters:

$$\alpha_2 = \frac{1 + \dfrac{2D_{opt}}{n(\alpha/\beta)_1}}{\dfrac{2D_{opt}^3}{n^2(\alpha/\beta)_1(\alpha/\beta)_2} + \dfrac{D_{opt}^2}{n(\alpha/\beta)_1} + \dfrac{2D_{opt}^2}{n(\alpha/\beta)_2} + D_{opt}} \tag{5}$$

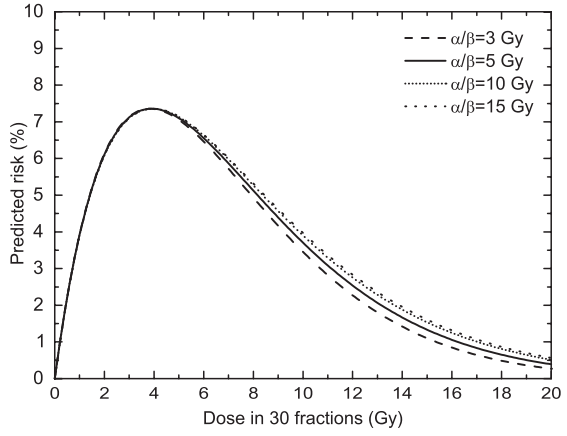

Figure 4. Risk predictions according to the LQ-based competition model for various assumptions regarding the α/β values. ($\alpha_1 = 0.05$ Gy^{-1}, $\alpha_2 = 0.25$ Gy^{-1})

where D_{opt} is the total "optimal dose" given in n fractions. It is important to mention here that according to Equation 5 the position of the maximum of the dose effect curve does not depend on the low dose slope of the process of inducing DNA mutations (α_1). Thus, it may seem that the position of the maximum of the dose response curve is mainly the effect of cellular survival.

Equation 5 also suggests that one can use the dose effect curve for cancer induction for the derivation of *in vivo* cell survival parameters. This is quite an interesting perspective as there is a need for *in vivo* parameters, because most of the cell survival parameters available now have been determined *in vitro* and they cannot always be used for modelling of the *in vivo* effects.

One important question arises with respect to the choice of parameters in Equation 5. While the $(\alpha/\beta)_2$ parameter describing cell survival is usually known from functional assays for acute or late effects following irradiation [22], little can be said about the $(\alpha/\beta)_1$ parameter describing the induction of DNA mutations. If the α/β value is a measure of the efficiency of the repair of sublethal DNA damage, as both DNA mutations and cell survival are related to DNA damage, one could in principle use the same value for $(\alpha/\beta)_1$ and $(\alpha/\beta)_2$. The matter needs further investigation, but if it proves to be true one can therefore use clinical data for cancer induction for easy determination of *in vivo* cell survival parameters.

Conclusions

We were able to describe the two main appearances of clinical data for cancer induction of secondary cancer following radiotherapy by using one single model based on the linear quadratic model with inducible repair (Equation 2). The appearances were found to be the manifestations of the parameters of the model. Thus, the levelling off appearance of the dose response curve could be either a sign of moderate inducible repair effect in cell survival (but weak for DNA mutations), or the effect of heterogeneity, or both. The maximum effect appearance encompasses all the other cases. As the levelling off appeared for relatively high radioresistances in both the described cases, we also concluded that its appearance in clinical data might be an indication of fairly resistant tissues. More research is however needed in order to clarify the details of the relationship between cell survival and DNA mutations. However, our modelling has suggested quite an interesting hypothesis which may be opened for investigation.

Furthermore, the results stress the importance of taking into account the details of the clinical delivery of dose in radiotherapy, mainly the fractionated character, as the findings of our study did not appear for single dose models.

We were also able to link clinical data for cancer induction to *in vivo* cell survival parameters that may be used for other applications such as the simulation of the tissue response to radiation for the biological evaluation of treatment plans.

Acknowledgements

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