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The estimation of second cancer risk following radiotherapy: a discussion of two models

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ABSTRACT

Purpose: Estimates of the probability of induction of second cancers following radiotherapy requires several modifications and extensions to the traditional linear dose-risk relationship. In this paper, two models, based on cell kill and an hypothetical "flat" risk response respectively, are modelled and compared using organ dose data from realistic simulations of radiotherapy of the prostate and larynx.

Materials and methods: A general model for cancer induction is used, which in principle takes into account the age profile of radiotherapy patients, a dose dependent DDREF and a general modifying factor which modifies induction probabilities at arbitrarily high doses. The model is applied to measurements of organ doses derived from simulation of a radical prostate treatment delivering 74 Gy to the target volume and a larynx treatment delivering 50 Gy to the target.

Results: A suggested set of realistic conditions gives a total second cancer induction risk of 2.2 - 8.2 cancers per 10^4 person years for the prostate and 4.4 - 4.7 cancers per 10^4 person years for the larynx, assuming a DDREF of 1. Widely varying values may be derived if certain key parameters in the models are varied.

Conclusion: Absolute determination of second cancer risk is subject to large uncertainties, but could be used to assess the relative dose and risk burden of alternative radiotherapy treatments, particularly those involving the same clinical site.

Keywords: Second cancers, radiotherapy dosimetry, radiotherapy treatment planning, radiation dose-risk relationships

INTRODUCTION

The induction of second cancers following radiotherapy is well documented [1], although the estimation of the probability of radiation carcinogenesis under these circumstances is far from straightforward. There are several reasons, however, why prospective estimates would be valuable.

For some cancers, there have been steady improvements in therapy leading to survival times exceeding the latent period for radiation carcinogenesis. For example, the 10-year survival rate for prostate cancer in the UK has increased from 20% to 50% over the last 30 years and the corresponding increase for breast cancer is from 40% to 70% in the same period [2]. In addition, the justification of medical exposures is a central tenet of radiation protection as formulated by ICRP [3]. In order to justify an exposure, both the benefits and the risks must be evaluated and compared. One of the risks

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involved with radiotherapy is that of second cancer induction after a latent period.

New developments in radiotherapy, which may lead to enhanced whole body exposure, are being implemented clinically. These include intensity modulated radiotherapy (IMRT) [4], tomotherapy [5] and the increasing use of imaging techniques for both verification and fraction-by-fraction guidance of dose delivery (image guided radiotherapy – IGRT), involving multiple CT examinations throughout the course of treatment, using both kilovoltage or megavoltage x-rays. The impact of various IMRT regimens is of particular interest, since the whole body dose burden for a radiotherapy treatment will be considerably greater than for any realistic combination of concomitant images. The outstanding question is to what extent is the conformation to the target volume and the associated sparing of adjacent normal tissue offset by the increased doses (and overall risk) to more remote parts of the body due to an increased leakage component (due to higher number of monitor units required) and a larger number of effective fields. Early work by Followill *et al*. [6] showed that considerable variation in whole body doses might be expected and Hall and Wuu have suggested that the introduction of IMRT might double the incidence of second cancers [7].

The situation is complicated by the fact that the administration of cytotoxic drugs has also been shown to result in induced cancers [1] and the combined effect of concomitant radiotherapy and chemotherapy is therefore difficult to evaluate.

THE VALIDITY OF EFFECTIVE DOSE IN A RADIOTHERAPY CONTEXT

In considering a framework for risk estimation, it is natural to consider dosimetric quantities which serve a similar purpose in other cases of human irradiation. In this respect, effective dose has been shown to be a useful quantity for combining organ doses from diverse exposure patterns at low doses encountered during personal monitoring and its prime function is to enable doses from external and internal sources to be combined for legislative purposes. It has also been used extensively to compare the dose burden for patients undergoing diagnostic radiological examinations. However, several problems exist if this concept is applied to radiotherapy exposures.

Effective dose, E, is defined as:

$$E = \sum_T w_T H_T \qquad (1)$$

with

$$\sum_T w_T = 1$$

where H_T is the equivalent dose and w_T is the tissue weighting factor. Tissue weighting factors are derived from detriment, a concept which may not be entirely relevant for cancer patients, for several reasons. First, the age profile of cancer patients is different from the population from which ICRP risk factors were derived. Second, the wide range of organ doses resulting from radiotherapy means that the use of a single-valued Dose and Dose Rate Effectiveness Factor (DDREF) may not be appropriate. Third, the incorporation of genetic effects and relative length of life lost may not be appropriate for patients who already suffer from cancer. For these reasons, this paper does not seek to define a quantity analogous to effective dose for radiotherapy purposes, but rather explores approaches to the estimation of the risk of cancer incidence.

THE DEPENDENCE OF RISK ON DOSE

Several organisations have developed estimates of stochastic risk following irradiation, based largely on analysis of the survivors of Hiroshima and Nagasaki (the Lifespan Study, LSS) [8]. In this paper, we do not attempt to reconcile these risk estimates, but rather choose those proposed by UNSCEAR [9] to use as examples, since they facilitate the comparison between the two particular models for high dose response which are examined below. When considering their application to cancer patients who have received radiotherapy, three major issues need to be addressed:

DOSE RESPONSE RELATIONSHIPS AT HIGH DOSES

At high doses, cell kill will become increasingly important and a simple model would suggest that cancer induction probabilities should decrease exponentially. In its simplest form, the risk of radiocarcinogenesis R_T to an organ T, following a dose D, may be described as:

$$R_T = f_{T,low} \cdot D \cdot e^{-\alpha_T D} \qquad (2)$$

where $f_{T,low}$ is the absolute excess risk per unit dose at low doses and is α_T a cell kill parameter. This model has been used by Schneider *et al*. [10] who derived values for α_T from a study of second cancer incidence in a population treated with radiotherapy for Hodgkin's disease. Modifications to this basic idea have been made by Wheldon *et al*. [11] who included mutation rate, intrinsic and mutational radiosensitivities and re-population effects in their two-stage model of radiocarcinogenesis. The introduction of more variables inevitably leads to a multiplicity of possible dose response relationships and furthermore, values for these parameters are not readily known *in vivo*. In fact, equation 2 describes the special case of Wheldon's model where no cell repopulation has taken place. However, these models, valuable as they are for exploring the relative effects of known parameters, do not explain several independent observations of induced cancers following radiotherapy where the risk appears to be approximately independent of dose from a few gray to several tens of gray. This has been discussed by Hall and Wuu [7] who selected studies on second cancers following radiotherapy for cancer of the cervix [12] and prostate [13]. These studies showed that relative risks

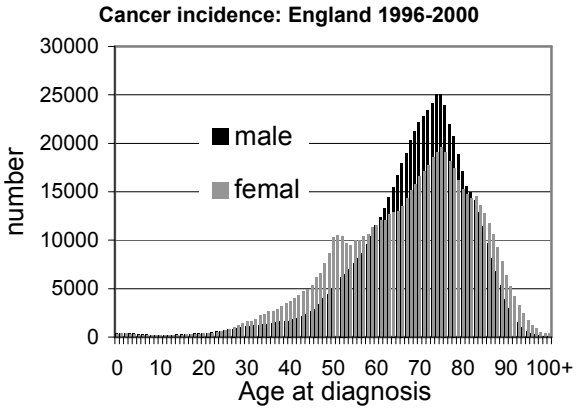

Figure 1 Incidence of cancer v. age at diagnosis in England (1996-2000). Source: UK Office for National Statistics.

were approximately constant in the ranges 30 - 80 Gy and 48 - 67 Gy respectively. A further post-radiotherapy study of tumour incidence as a function of dose at the site of the second cancer [14] showed that approximately 35% of second cancers arose at sites which had received 10 - 30 Gy, with a small number at sites of higher doses up to 65 Gy. As Hall and Wu suggest, a constant risk with increasing dose represents an extreme possibility, and intuitively we may imagine that some risk reduction with dose is plausible, although the form of the functions for each organ or tissue is currently unknown.

A comprehensive study of risk factors derived from cohorts of radiotherapy patients and comparison with similar cohorts derived from the LSS [1] also showed excess risks at high doses. Excess relative risks from the radiotherapy groups were found to be either less than or comparable to those from the LSS. In some cases, the differences were not statistically significant because of the subdivision of data into individual cancer sites. Although this work showed that risk factors derived from the LSS may be used with caution in radiotherapy, effects of cell kill are difficult to predict with accuracy and uncertainties are large.

DOSE AND DOSE RATE EFFECTIVENESS FACTOR (DDREF)

DDREF is given by:

$$DDREF = \frac{\alpha_{high}}{\alpha_{low}} \quad (3)$$

where α_{high} is the slope of a linear relationship between high dose LSS data and dose, where the line is constrained to pass through the origin, and α_{low} is the gradient of the dose response curve at very low doses. Thus the DDREF is essentially a factor which is used to derive the hypothetical low dose slope of the dose-risk curve from the high dose LSS data.

A range of values for DDREF, including many derived from animal studies, has been discussed by several groups [15, 3]. Currently, it is usually assumed that the DDREF = 2 [3] and UNSCEAR [16] have suggested that this value is adopted (i) for doses < 200 mGy, for all dose rates (i.e. acute doses) and (ii) for dose rates < 0.1 mGy min^{-1}, for all doses, (i.e. chronic doses). For doses ≥ 200 mGy and dose rates ≥ 0.1 mGy min^{-1}, it is implied that DDREF = 1.

The choice of two distinct doses and dose-rate related values for the DDREF implies that the high dose (≥ 200 mGy) and low dose (< 200 mGy) regions are assumed not to co-exist within the same patient or subject. However, this is clearly not the case in radiotherapy where organ doses ranging from a few milligray to tens of gray may result, thus straddling the boundary between DDREF = 1 and DDREF = 2. Even considering a single fraction delivering 2 Gy to the target, organs and tissues close to the target volume will receive doses in excess of 200 mGy, but distant organs will receive much lower doses. The integration time for the dose rate criterion is approximately one hour, so the boundary between DDREF = 1 and DDREF = 2 is 6 mGyh^{-1}, and based on this figure, both values of DDREF may be invoked following a single fraction. Thus the use of a discontinuous DDREF, as currently recommended, is counter-intuitive and inapplicable to the radiotherapy case. A DDREF which varies continuously with dose between defined limits might be more realistic, although both DDREF = 1 and DDREF = 2 have been used in the radiotherapy context, the latter based on the argument that all fractionated radiotherapy is protracted compared with the instantaneous irradiation of the LSS subjects.

AGE PROFILE OF THE EXPOSED POPULATION

The age profile of cancer incidence in the UK is shown in figure 1 (Rowan, private communication) and it may be assumed that the distribution for patients receiving radiotherapy is similar. This distribution may be different from those used to derive cancer incidence estimates from the LSS data. Age related risk factors have been addressed by several authors (e.g. [15]) who show that the cancer induction risk decreases with increasing age at exposure. Whilst this implies that the use of LSS-derived risk factors may overestimate risks to most cancer patients, it is important to realise that the converse (i.e. higher risks for younger patients) may be equally important for the small fraction of patients receiving radiotherapy in childhood, particularly those with good prognoses, who may be expected to survive well into adulthood.

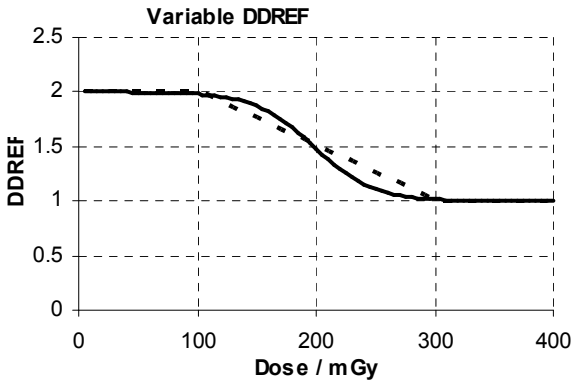

Figure 2 Hypothetical sigmoidal (solid line) and linear (dotted line) functions to describe a non bi-modal DDREF.

MODELS FOR RISK ESTIMATION

It is clear from the preceding discussion that a linear relationship between risk and dose, a bi-valued DDREF and an implicit age-independence of low dose risk factors are inappropriate for radiotherapy purposes. A modified framework for risk estimation is thus suggested, which acknowledges a non-linear response at high doses, a variable DDREF and the age profile of cancer patients.

Consider a critical organ, T, for which a low-dose radiocarcinogenic risk per unit dose, $f_{T,low}$, has been identified. We assume that we may sub-divide this organ into a total of N_T independent volumes i, for each of which the dose $D_{T,i}$, are known, thus allowing for arbitrary dose heterogeneity.

The carcinogenic risk (excess absolute risk) to the whole organ, R_T, may be given by:

$$R_T = \alpha_{pop} \cdot f_{T,low} \sum_{i=1}^{N_T} \frac{m_i \cdot g_T(D) \cdot D_{T,i}}{DDREF(D)} \quad (4)$$

where

$f_{T,low}$ is the absolute excess risk per unit dose at low doses, given, for example, by UNSCEAR [9].

a_{pop} is a dimensionless factor which allows for the age dependence of $f_{T,low}$

m_i is the mass fraction corresponding to each of the N_T volumes which comprise the organ. Thus:

$$\sum_{i=1}^{N_T} m_i = 1$$

$g_T(D)$ is a dose-dependent multiplicative factor which modifies $f_{T,low}$ at high doses (for example to account for cell kill). DDREF is the dose and dose rate effectiveness factor.

Finally, the carcinogenic risk to the individual, R_{total}, is given by summing the risks to all irradiated organs:

$$R_{total} = \sum_{all\ T} R_T \quad (5)$$

In this paper, we compare two models for $g_T(D)$, based on cell kill [10] and "constant" risk [7], respectively, by using organ dose data from simulated prostate and larynx irradiations. Both models can draw support from epidemiological data in restricted circumstances, but only for the follow-up of certain radiotherapy treatments and for the induction of cancers in some organs.

Cell kill models

Here, the term $g_T(D)$ reflects an appropriate cell kill model, the simplest being $g_T(D) = e^{-\alpha_T D_{T,i}}$, i.e.

$$R_T = \alpha_{pop} \cdot f_{T,low} \sum_{i=1}^{N_T} \frac{m_i \cdot e^{-\alpha_T D_{T,i}} \cdot D_{T,i}}{DDREF(D)} \quad (6)$$

Schneider *et al*. [10] have described this approach in which $a_{pop} = 1$, $DDREF(D) = 1$ and $m_i = 1/N_T$, for all i (i.e. a uniform spatial sampling of the organ). This gives:

Schneider *et al*. have defined the term in brackets as the Organ Equivalent Dose (OED). This is the dose which, if given uniformly to an organ, would result in the same carcinogenic risk as the non-uniform irradiation. At low doses, the exponential term approximates to unity and the term in brackets is simply the average organ dose. They have derived values for α_T for several critical organs from observations of cancers following radiotherapy for Hodgkin's disease.

"Flat" dose response model

The extreme possibility described by Hall and Wuu [7] is modelled as follows.

We assume that risk is a linear function of dose up to some dose D_c , is constant thereafter and is zero above a dose D_{max}. Thus $g_T(D)$ is given by:

$$\begin{aligned} g_T &= 1 && 0 \le D_T \le D_c \\ g_T &= D_c / D_T && D_c < D_T \le D_{\max} \\ g_T &= 0 && D_{\max} < D_T \end{aligned} \quad (8)$$

Following [7], it might be reasonable to choose $D_c = 4$ Gy , following the shape of the solid cancer dose response function from the LSS (e.g [8]) and $D_{max} = 60$ Gy, derived from the highest doses following which second cancers have been recorded [1, 12-14].

a_{pop}: Muirhead *et al*. [15] have proposed age dependent risk factors for radiation-induced fatal cancer and it is suggested here that these are represented by three age bands, 0 - 19, 20 - 49 and 50+ years, for which the average values of fatal cancer risk, normalised to 5.9% Gy^{-1}, are 1.8, 0.8 and 0.4 respectively. It is assumed that these factors for cancer mortality will be equally applicable to cancer incidence.

DDREF(D): There are many possibilities for refining the definition of the DDREF, and the choice depends, to a large extent, on the definition of what is meant by "low" doses and dose rates. To be consistent with UNSCEAR advice [16], $DDREF(D) = DDREF_{max}$ for low doses << 200 mGy and should be unity for doses > 200 mGy. There are numerous empirical functions

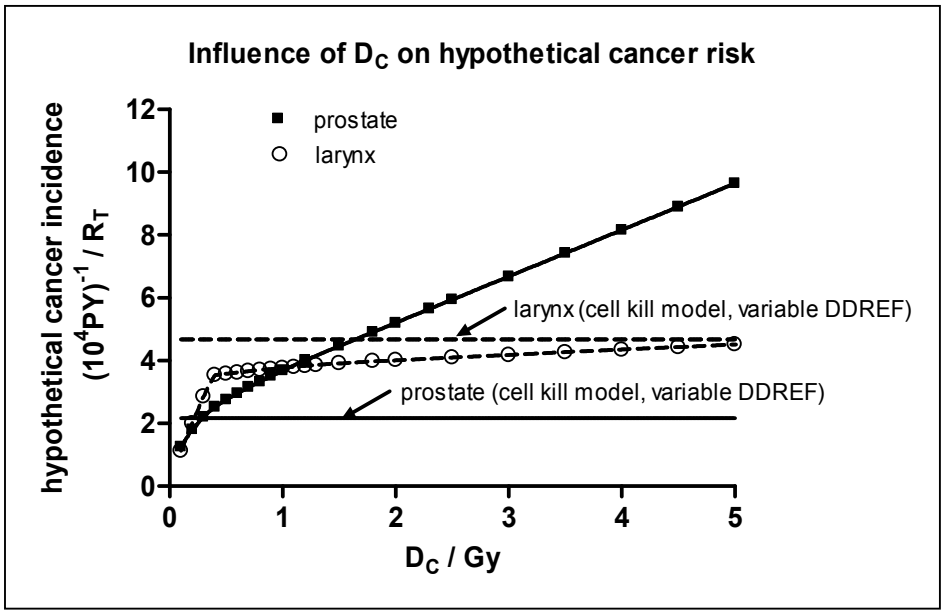

Figure 3 R_T as a function of D_c, the dose at which it is assumed that a linear risk-dose response becomes dose-invariant. Closed squares are results for the prostate simulation and open circles for the larynx simulation. Values of R_T for the cell kill model for larynx and prostate simulations are given by dotted and solid lines respectively.

which would fulfil these criteria, for example the family of sigmoid functions given by

$$DDREF(D) = 1 + \frac{1}{1 + k_1 \exp(k_2 D)} \quad (9)$$

This is illustrated in figure 2 (solid line) for $k_1 = 4.10^{-4}$ and $k_2 = 4.10^{-2}$ Gy^{-1}.

The choice of k_1 and k_2 are entirely arbitrary and given the large uncertainties in the estimates of DDREF, such complexity is hardly justified. A simpler, albeit discontinuous, empirical function describes a simple linear fall in DDREF from $DDREF_{max} = 2$ to DDREF = 1 as follows:

$$\begin{aligned} DDREF &= 2 && 0 \le D_T \le D_0 \\ DDREF(D_T) &= \\ & DDREF_{\max} - \frac{(D_T - D_0)}{(D_1 - D_0)} && D_0 < D_T < D_1 \\ DDREF(D_T) &= 1 && D_1 \le D_T \end{aligned} \quad (10)$$

Figure 2 (dotted line) shows this function, in which $D_0 = 100$ mGy, and $D_1 = 300$ mGy, so that DDREF = 1.5 at the transition dose suggested by UNSCEAR [16].

COMPARISON OF RISK ESTIMATE MODELS FOR SIMULATED RADIOTHERAPY OF THE PROSTATE AND LARYNX

A detailed description of the simulation of radiotherapy treatments of the prostate and larynx has previously been given [17, 18]. An anthropomorphic phantom loaded with thermoluminescent dosimeters (TLD-100) was irradiated according to realistic treatment plans and doses to critical organs and tissues measured and scaled to give the doses which would have been received following delivered target doses of 74 Gy (prostate: 3-field, 15 MV, Siemens Primus H1 linear accelerator) and 50 Gy (larynx: 2-field 6 MV, Siemens Primus H1 linear accelerator). A neutron component was included for the prostate treatment. For organs close to the target volume, where part of the organ received doses > 4 Gy, sub-division of the organ according to equation 4 was invoked. This was also invoked for distributed organs such as skin and bone surfaces. For organ doses < 4 Gy, mean organ doses have been used in equation 4. In practice, the sub-volumes were taken as the volumes of the organ within each adjacent slice of the RANDO phantom, since the mass fractions for these volumes were known [19]. Although this sampling is coarser than could be achieved by deriving the organ doses from the output of a treatment planning system, it will suffice to compare the models of radiocarcinogenesis described above. For simplicity, a_{pop} was assumed to be unity for the purposes of comparing the two models.

Values for the parameters in equation 4 are given in table 1.

RESULTS

Excess absolute risks of carcinogenesis are given in tables 2 and 3 for prostate and larynx treatments

respectively. They have been calculated for a variable DDREF and also for the case of DDREF = 2.

Figure 3 shows R_T as a function of D_c, the dose at which it is assumed that a linear risk-dose response becomes dose-invariant.

DISCUSSION AND CONCLUSIONS

The estimation of the probabilities of induced cancers following radiotherapy is in its infancy. Uncertainties exist in several parameters and relationships, for example, risk as a function of age, risk modification as a function of disease state, pre-disposition to cancer induction and choice of risk model as a function of organ dose. The situation is further complicated by the need to use, as a starting point, risk factors derived for the LSS, i.e. for a wholly different population. However, in this respect, the values of α_T in the cell kill model of Schneider *et al*. [10] is worthy of further development because they are derived from a radiotherapy population. In this paper, we have highlighted the inherent problems by outlining a general model for second cancer induction and calculating second cancer risks for two very different derived models, one based on cell kill and one based on epidemiological suggestions of a "flat" dose response.

In the latter, a critical parameter is D_c, the dose at which it is postulated that the assumed linear relation between second cancer risk and dose becomes a near flat response up to high doses. Figure 3 shows that R_T increases from 3.68 Gy at $D_c = 1$ Gy to 9.64 Gy at $D_c = 5$ Gy for prostate treatment, where the overall risk is strongly dependent on the relatively high bladder risk factor and high bladder dose, $D_{bladder}$. This means that R_T continues to increase with increasing values of $D_c < D_{bladder}$. In the cell kill model, the risk of induced bladder cancer is negligible. This is due partly to the high value of α_T [10] but also to the coarse dosimetric sampling resulting from the use of an anthropomorphic phantom. This has resulted in all the bladder locations receiving high doses (18 - 67 Gy), whereas it would be more realistic to assume that certain portions of the bladder wall would receive lower doses such that the effects of cell kill would not be so severe and increase the carcinogenic risk. In practice, the incidence of bladder cancer following prostate radiotherapy is significant [13]. These authors [13] have also estimated a risk of 1 per 1220 PY for the absolute numbers of second solid tumours associated with prostate radiotherapy (all years after diagnosis). This corresponds to 8.2 $(10^4 PY)^{-1}$ in figure 3, again demonstrating that the cell kill model cannot be tested adequately because of the coarse dosimetric sampling referred to above. The "flat" dose response model, on the other hand, gives second solid tumour incidence in broad agreement with [13], for $D_c \sim 4$ Gy.

In contrast, for the larynx case, the increase of R_T with increasing D_c is not so marked for $D_c > 0.4$ Gy. This is because the critical organs (thyroid, mouth, pharynx) have lower risk factors than the bladder, and the comparatively smaller volumes which exceed doses > D_c provide proportionately smaller contributions to the overall risk. Compared with the variable DDREF model, the assumption of DDREF = 2 will reduce the estimated risks by approximately a factor of two, since most organs receive doses which are sufficiently low, so that the variable DDREF approximates to DDREF = 1.

Thus the choice of model within the boundaries of those described here is crucial, with ranges of R_T by factors of 5 and 2 for prostate and larynx simulations respectively.

Treatment planning for modern radiotherapy can probably do no more at the present than limit the doses to critical organs outside the target volume to avoid deterministic effects. The current state of knowledge of organ risk factors for a radiotherapy population, and for high doses greater than a few gray, means that formal algorithms for quantitatively optimising stochastic risks may not yet be feasible.

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Table 1 Values for $f_{T,low}$, α, D_c, D_{max}, D_0, and D_1 used in the calculation of radiocarcinogenic risk

Organ or tissue	**$f_{T,low}$ [9] $(10^4 PYGy)^{-1}$**	**α_T [10] (Gy^{-1})**
Bladder	1.62	1.592
Colon	2.71	0.24
Lungs	8.27	0.129
Stomach	6.15	0.149
Liver	1.50	0.487
Thyroid	0.13	0.033
Skin	0.58	0.047
Bone surface & connective tissue	0.11	0.033
Prostate	0.44	0.804
Mouth and pharynx	0.23	0.017
Pancreas	0.24	0.092

D_c = 4 Gy and D_{max} = 70 Gy
For the variable DDREF, D_0 = 100 mGy and D_1 = 300 mGy

Table 2 Calculation of excess absolute risk to critical organs and tissues for a simulated prostate treatment

Organ or tissue	**Organ dose (Gy)**	**R_T $(10^4PY)^{-1}$**	**R_T $(10^4PY)^{-1}$**	**R_T $(10^4PY)^{-1}$**
		cell kill model	**flat response model**	**cell kill model**
		Variable DDREF		**DDREF = 2**
Bladder	18 - 66	< 0.0001	5.05	< 0.0001
Lower large intestine (colon, rectum)	0.3 - 60	1.060	1.99	0.530
Lungs	0.102	0.420	0.426	0.418
Stomach	0.138	0.461	0.471	0.417
Liver	0.120	0.089	0.095	0.085
Thyroid	0.082	0.005	0.005	0.005
Skin	0.0009 - 1.4	0.093	0.098	0.050
Bone surface & connective tissue	0.002 - 0.52	0.003	0.003	0.002
Prostate	n/a			
Mouth and pharynx	0.053	0.006	0.006	0.006
Pancreas	0.147	0.020	0.020	0.017
Total		2.16	8.16	1.53

Table 3 Calculation of excess absolute risk to critical organs and tissues for a simulated larynx treatment

Organ or tissue	**Organ dose (Gy)**	**RT $(10_4PY)^{-1}$**	**RT $(10_4PY)^{-1}$**	**RT $(10_4PY)^{-1}$**
		cell kill model	**flat response model**	**cell kill model**
		Variable DDREF		**DDREF = 2**
Bladder	0.013	0.01	0.01	0.010
Lower large intestine (colon, rectum)	0.018	0.02	0.02	0.025
Lungs	0.377	2.97	3.11	1.48
Stomach	0.051	0.15	0.16	0.15
Liver	0.0059	0.04	0.04	0.04
Thyroid	1.3 - 56.3	0.86	0.38	0.43
Skin	0.0026 - 23.9	0.14	0.10	0.07
Bone surface & connective tissue	0.0024 - 1.93	0.01	0.0085	0.0045
Prostate	0.013	0.0028	0.0028	0.0028
Mouth and pharynx	0.93 - 6.63	0.45	0.51	0.23
Pancreas	0.042	0.01	0.01	0.01
Total		4.68	4.35	2.46