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ORIGINAL PAPER

Track-event theory of cell survival with second-order repair

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Abstract When fractionation schemes for hypofractionation and stereotactic body radiotherapy are considered, a reliable cell survival model at high dose is needed for calculating doses of similar biological effectiveness. In this work, a simple model for cell survival which is valid also at high dose is developed from Poisson statistics. It is assumed that a cell is killed by an event that is defined by two double-strand breaks on the same or different chromosomes. Two different mechanisms can produce events. A one-track event is always represented by two simultaneous double-strand breaks. A two-track event results in one double-strand break. Therefore, at least two two-track events on the same or different chromosomes are necessary to produce an event. It is assumed that two double-strand breaks can be repaired with a certain repair probability. Both the one-track events and the two-track events are statistically independent. From the stochastic nature of cell killing which is described by the Poisson distribution, the cell survival probability was derived. The model was fitted to experimental data. It was shown that a solution based on Poisson statistics exists for cell survival. It exhibits exponential cell survival at high dose and a finite gradient of cell survival at vanishing dose, which is in agreement with experimental cell studies. The model fits the experimental data as well as the LQ model and is based on two free parameters. It was shown that cell survival can be described with a simple analytical formula on the basis of Poisson statistics. This solution represents in the limit of large dose the typical exponential behavior and predicts cell survival as well as the LQ model.

Keywords Cell survival · Poisson statistics · Linear-quadratic model

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Introduction

When alternative fractionation schemes in radiotherapy are considered, a reliable cell survival model is needed for calculating doses of similar biological effectiveness. This is in particular of interest with increasing importance of hypofractionation and stereotactic body radiotherapy for which such a survival model must be applicable to doses up to approximately 20 Gy (Brenner 2008; Garcia et al. 2006). The tool most commonly used for quantitative predictions of alternative dose fractionations is the linear-quadratic (LQ) formalism (Lea and Catcheside 1942; Kellerer and Rossi 1972; Douglas and Fowler 1976; Dale 1985; Fowler 1989). In radiotherapeutic applications, the LQ formalism is now commonly used for calculating isoeffect doses for different fractionation schedules. However, a characteristic of the LQ formalism is that the dose–response curve bends continuously on the log-linear plot even at high dose. This does not coincide with what is observed experimentally in many clonogenic cell survival studies where the dose–response relationships exhibit an exponential decrease in survival at high dose, which more closely approximates a straight line on the log-linear plot (Elkind and Sutton 1959; Atwood and Norman 1949; Carlone et al. 2005; Puck and Markus 1956; Astrahan 2008).

One alternative methodology which describes cell killing exhibiting an exponential decrease at large dose is the

"single-hit multitarget formula" (Alper 1979). For this model, it is assumed that a cell is inactivated only when at least n targets in the cell are hit. The major drawback of this model is that the cell survival curve at low dose exhibits a vanishing gradient at low dose, which is not in agreement with experimental data.

Another model is the "universal survival curve" (Park et al. 2008), which is the combination of a LQ model with a linear extension at large dose. This model is essentially an empirical description that fits clinical data well, but is not based on a mechanistic understanding of the underlying processes that lead to cell killing.

Recently, Ekstrand (2010) was re-examining the Hug–Kellerer (Hug and Kellerer 1963) model of cell survival and established the relationship between this model and the LQ model. This model fits well published cell survival curves over a wide dose range. However, this is achieved by introducing a third fitting parameter.

In a previous work (Besserer and Schneider 2014), a simple track-event model of cell survival was developed from Poisson statistics. The model evolved from a few basic assumptions and is based on only two parameters. It exhibited exponential cell survival at high dose and a finite gradient of cell survival at vanishing dose. The model included full repair of one double-strand break (DSB) due to a two-track event, which we call here first-order repair. However, this simple track-event model represented the shape of some cell survival data insufficiently.

In this work, the track-event model is extended by including repair of two simultaneous DSBs on one or more chromosomes. The goal was that only two parameters are used to describe repair and cell killing by relating the probabilities for one-track events (OTE) and two-track events (TTE) for various cell lines relative to each other. It is found that this two-parameter cell-killing model explains cell survival curves as well as the LQ model by exhibiting exponential cell survival at high dose. In contrast to other models, it evolves from a mechanistic description of the involved processes, and the two model parameters are related to probabilities describing the biological and physical processes.

Materials and methods

It is assumed that the critical lesion of energy deposition is chromosomal DNA. Significant result of energy deposition is a DSB of the DNA. The assumptions regarding energy deposition are as follows (Sachs et al. 1997):

(a) A track is a deposition of energy caused by the passage of charged or uncharged primary high-energy particles as well as all resulting secondary particles.
(b) A track can produce one or more DSBs by direct ionizations ($\sim 10^{-15}$ s) or by the production of free radicals in the vicinity of the DNA ($\sim 10^{-12}$ s).
(c) One DSB is non-lethal.
(d) An event is defined by two DSBs on the same or different chromosomes that can be lethal or can be repaired. An event can result in direct lethal damage or lethal binary misrepair by the formation of chromosome aberrations as dicentrics or centric and acentric rings.

Two different mechanisms can produce events: OTE or TTE. They are defined as follows:

1. The target for an OTE is always an event represented by two DSBs on the same or different chromosomes.
2. The target for a TTE is one DSB. It is called TTE, since at least two TTEs on the same or different chromosomes are necessary to produce an event.
3. Repair: it is assumed that DSBs resulting from one TTE are always repaired. Two DSBs on the same or different chromosomes can lead to the formation of non-lethal chromosome aberrations as, e.g., symmetrical translocations or can be repaired with a certain repair probability R;
4. Both the one-track mechanism and the two-track mechanism are statistically independent events in the terminology of nanodosimetry.

The distribution of potential OTEs and TTEs is displayed in Fig. 1. With (4), a stochastic nature of cell killing is assumed, which can be described by the Poisson distribution when it is assumed that the number of irradiated cells is large and the probability for hitting the target is small. The cell survives when there is no OTE or at most one TTE as shown in Fig. 1. Survival is also possible when cells with two DSBs resulting from one OTE or two TTEs are repaired. The number of cells with no events (no OTE and no TTE) can be calculated from Poisson statistics to be

$$N^{(0)} = N_0 \cdot \mathrm{e}^{-x}, \tag{1}$$

where N_0 is the number of original cells and x the mean number of hits. The number of cells that receive one hit is

$$N^{(1)} = N_0 \cdot x \cdot \mathrm{e}^{-x}. \tag{2}$$

The number of cells that receive two hits is

$$N^{(2)} = N_0 \cdot \frac{x^2}{2} \cdot \mathrm{e}^{-x}. \tag{3}$$

Since OTEs and TTEs are according to (4) statistically independent, the probability for both can be described by independent Poisson distributions. When the probabilities

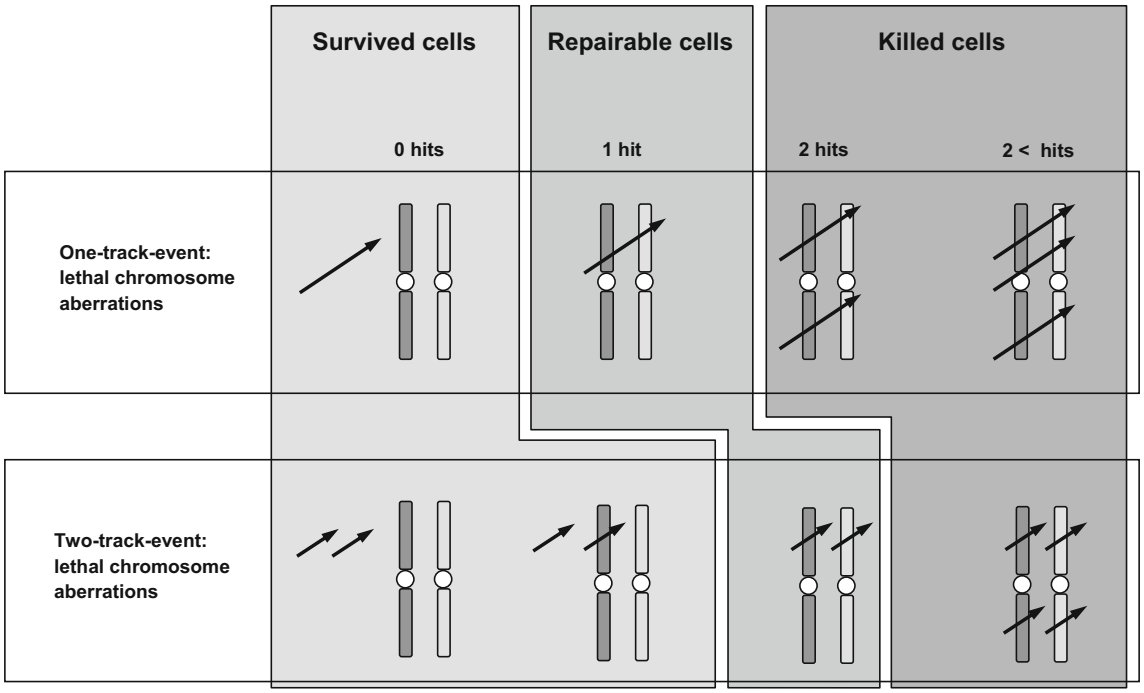

Fig. 1 Sketch of the distribution of chromosomal aberrations induced by one-track and two-track events. It is shown which events lead to cell survival and cell killing, respectively. For clarity, not all reactions and processes after a DSB which can lead finally to lethality are shown

for OTEs are determined, a hit in Eqs. (1)–(3) is an event, i.e., two lethal DSBs on the same or different chromosomes. In contrast, a hit is synonymous with a single DSB when we apply Eqs. (1)–(3) for examining TTEs. It can be assumed that the mean number of hits x in the Poisson distribution is then the mean number of lethal events for the OTE statistic or the mean number of DSBs for the TTE statistic. For both, it can be assumed that x is proportional to dose D. However, since DSBs and lethal events occur with different probabilities, the proportionality constant will be different. Therefore, we write $x = p{\cdot}D$ for OTE and $x = q{\cdot}D$ for TTE, respectively.

In case of OTEs, it is assumed that the cell survives with a probability S_{OTE} when there is no hit or when one hit (resulting in two DSBs) is repaired

$$S_{\mathrm{OTE}} = P_{\mathrm{OTE}}(0 \cup R1) = P_{\mathrm{OTE}}(0) + R \cdot P_{\mathrm{OTE}}(1), \tag{4}$$

where $R1$ represents a repaired one hit and R represents the probability for either repairing two DSBs or the formation of non-lethal chromosomal aberrations.

A cell survives a TTE with the probability S_{TTE} when there is at most one hit or when two hits (resulting in two DSBs) are repaired

$$\begin{aligned} S_{\mathrm{TTE}} &= P_{\mathrm{TTE}}(0 \cup 1 \cup R2) \\ &= P_{\mathrm{TTE}}(0) + P_{\mathrm{TTE}}(1) + R \cdot P_{\mathrm{TTE}}(2), \end{aligned} \tag{5}$$

where $R2$ represents repaired two hits and $P_{\mathrm{TTE}}(0)$, $P_{\mathrm{TTE}}(1)$, and $P_{\mathrm{TTE}}(2)$ are the probabilities for no, one, or two TTEs, respectively. The total survival probability is then

$$S = S_{\mathrm{OTE}} \cdot S_{\mathrm{TTE}}. \tag{6}$$

It is further assumed that the probability for survival is proportional to the ratio of the number of survived cells relative to the number of total cells N_0. The probability that a cell survives becomes then by using Eqs. (1), (2), (3), and (6)

$$\begin{aligned} S = e^{-(p+q)\cdot D}\Bigg(1 + D \cdot (q + R \cdot p) + D^2 \\ \cdot \left(\frac{R \cdot q^2}{2} + R \cdot p \cdot q\right) + D^3 \cdot \frac{R^2 \cdot q^2 \cdot p}{2}\Bigg). \end{aligned} \tag{7}$$

We hypothesize here that the probabilities p and q for OTEs and TTEs are not independent from each other. Although the absolute probabilities p and q will depend on the three-dimensional structure of the cell nuclei and the interphase chromosome territories as, for example, the number of chromosomes, the dimensions of the chromosome territories, the looping probabilities of the chromatin fiber, and many others, the ratio of p and q should be solely dependent on the fundamental organization of the chromatin fiber. Therefore, we hypothesize that all cells that have the same basic chromatin structure in common are subject to the same p/q ratio. In human cells, the tetranucleosome is the basic component of the chromatin fiber (Schalch et al. 2005; Woodcock 2005). Thus, the p–q ratio

should depend solely on the distribution of DNA in the tetranucleosome, and we can define

$$\varepsilon = \frac{p}{q}. \tag{8}$$

Thus, the proportionality constant ε can be determined in principle from the geometrical structure of the tetranucleosome. However, relation (8) will depend on other variables as, for example, radiation quality. Therefore, in this work, we focus exclusively on photon radiation.

When ε is fixed, the cell survival probability of Eq. (7) becomes simply a function of the two parameters R and q

$$S = e^{-(1+\varepsilon)\cdot q\cdot D}\left(1 + D\cdot q\cdot(1+\varepsilon\cdot R) + D^2\cdot q^2\left(\frac{R}{2}+\varepsilon\cdot R\right) + D^3\cdot q^3\cdot\frac{R^2\cdot\varepsilon}{2}\right) \tag{9}$$

We have examined the validity of the cell survival model developed in this work on 42 sets of cell survival data (Garcia et al. 2006; Miyakawa et al. 2014; Park et al. 2008; Puck and Markus 1956; Ruiz de Almodóvar et al. 1994; Tonkin et al. 1989; Hall et al. 1986; Sullivan et al. 1996; Steel et al. 1987; Algan et al. 1996; DeWeese et al. 1998; Leith et al. 1993; Suzuki et al. 1997; Tsuboi et al. 1998; Tsuchida et al. 1998; Kamlah et al. 2011; Furusawa et al. 2000; Chapman et al. 1978; Stenerlöw et al. 1995; Persson et al. 2002; Ito et al. 2006). We have chosen published survival curves of human cell lines that were irradiated with Co-60, Cs-137, or X-ray radiation of at least 220 kV energy and dose rates between 0.7 and 2.0 Gy/min. The data fits were produced with a nonlinear least-squares algorithm with the software package PV Wave (PV-Wave Advantage, PV-Wave Command Language, version 9.01—Numerics, Inc.—2008) using the experimental errors (were available) as weights. When no errors were provided, an exponential weighting of the data points was used, assuming a constant relative error over the complete dose range. To test for statistical significance, the t test was applied.

Results

It is assumed that the parameter ε is constant for a specific radiation quality and for cells with the same fundamental components of chromatin organization. To obtain ε, the 42 sets of human cell survival data were fitted to Eq. 7, and from the fitted values for p and q, ε was determined. The probability p for an OTE should be smaller than q for a TTE; thus, for the fits, it was assumed that p is always smaller than q. Although a three-parameter fit to the survival data is hardly significant, we believe that the average p/q ratio over the 42 human cell lines yields an appropriate estimate of ε. The results of the fits are listed in Table 1. The resulting averaged ε is 0.64 with an error of 0.32 (one standard deviation).

The obtained $\varepsilon = 0.64$ was then used to fit the two-parameter model (Eq. 9) to the survival data. In addition, the LQ model was fitted using the same experimental data, weightings, and fitting procedure. The obtained parameters p and q and α and β, respectively, are listed in Table 1 together with the corresponding errors and the p value. If a confidence level of 95 % is assumed for both model parameters, then 36 out of the 42 data sets were fitted with statistical significant parameters p and q. The LQ model was significant for 32 data sets on a 95 % confidence level. For the figures, the fitted cell lines were grouped into seven types. In Fig. 2, the prostate cell lines with the corresponding fits to Eq. 9 are shown; in Fig. 3 the glioma cell lines; in Fig. 4 the lung cell lines; in Fig. 5 the cervix cell lines; in Fig. 6 the fibroblast, skin, and melanoma cell lines; in Fig. 7 the breast, bladder, and colon cell lines; and in Fig. 8 the thyroid, salivary gland, leukemia, and embryo cell lines.

From Eq. 9, the isoeffect formula can be calculated to transform different fractionation schedules. If we assume two fractionation schedules, one with a dose per fraction df_1 and a total dose D_1, then the total dose D_2 for a dose per fraction df_2 can be calculated with

$$D_2 = \frac{(1+\varepsilon\cdot q)+\frac{1}{df_1}\ln\left\{\left(1+q\cdot df_1+\frac{1}{2}\cdot R\cdot q^2\cdot df_1^2\right)(1+\varepsilon\cdot R\cdot q\cdot df_1)\right\}}{(1+\varepsilon\cdot q)+\frac{1}{df_2}\ln\left\{\left(1+q\cdot df_2+\frac{1}{2}\cdot R\cdot q^2\cdot df_2^2\right)(1+\varepsilon\cdot R\cdot q\cdot df_2)\right\}}D_1 \tag{13}$$

Discussion and conclusions

A solution of cell survival derived from Poisson statistics for one- and two-track events using the simple assumptions (1)–(4) was determined and fitted to experimental data of 42 different cell lines. The model derived in this work exhibits exponential cell survival at high dose and a finite gradient of cell survival at vanishing dose. The solution, which uses only two free parameters, was compared to the fits of the LQ model. Both models describe the experimental data satisfactorily with 36 statistically significant results for the model derived in this work and 32 for the LQ formalism, respectively.

The cell survival model derived in this work exhibits several advantages when compared to the LQ formalism. First of all, it evolves from a pure mechanistic approach, and the parameters ε, q, and R can be related directly to biophysical characteristics of the cells. The repair capacity R can be assumed to be dependent on cell type and dose rate, but independent of radiation quality. The parameter ε

Table 1 List of fit parameters to experimental cell survival data for the different cell lines

Author/ref.	Cell type	Cell line	Fit to Eq. 7			$\varepsilon = p/q$	Fit to Eq. 9		p (q)	p (R)	Fit to LQ model			p (β)
			p	q	R		q	R			α	β	p (α)	
Garcia et al. 2006	Glioma	U373MG	0.276	0.435	0.660	0.63	0.429	0.668	<0.01**	<0.01**	0.143	0.023	<0.01**	<0.01**
	Prostate	CP3	0.242	0.800	1.000	0.30	0.628	1.000	<0.01**	<0.01**	0.053	0.060	<0.01**	<0.01**
	Prostate	DU145	0.186	0.436	0.379	0.43	0.392	0.472	<0.01**	<0.01**	0.201	0.015	<0.01**	<0.01**
Miyakawa et al. 2014	Breast	EMT6	0.394	0.568	0.850	0.69	0.587	0.841	<0.01**	<0.01**	0.141	0.041	<0.05*	<0.01**
Park et al. 2008	Lung	H460	0.181	0.571	1.000	0.32	0.457	1.000	<0.01**	<0.01**	0.087	0.023	<0.01**	<0.01**
Puck and Markus 1956	Cervix	HeLa	0.801	0.815	0.653	0.98	0.976	0.572	<0.01**	<0.01**	0.404	0.106	<0.01**	<0.01**
Ruiz de Almodóvar et al. 1994	Bladder	RT112	0.345	0.447	0.840	0.77	0.482	0.810	<0.01**	<0.01**	0.187	0.020	<0.01**	<0.01**
Tonkin et al. 1989	Cervix	HX156c	0.398	0.574	0.745	0.69	0.592	0.733	<0.01**	<0.01**	0.236	0.032	<0.01**	<0.01**
	Cervix	NX160c	0.845	0.846	0.881	1.00	1.030	0.804	<0.01**	<0.01**	0.291	0.124	<0.01**	<0.01**
Hall et al. 1986	Fibroblast	AG1522	0.391	0.392	0.242	1.00	0.453	0.112	<0.05*	0.82	0.373	0.016	<0.01**	<0.05*
Sullivan et al. 1996	Lung	A549	0.433	0.436	0.686	0.99	0.526	0.605	<0.01**	<0.01**	0.238	0.026	<0.01**	<0.01**
	Lung	NCI-H69	0.756	0.757	0.000	1.00	0.987	0.000	0.86	1.00	1.059	0.000	<0.01**	1.00
	Lung	NCI-H460	0.323	1.142	1.000	0.28	0.885	1.000	<0.01**	<0.05*	0.000	0.140	1.00	<0.01**
Steel et al. 1987	Skin	HX118	0.502	0.503	0.403	1.00	0.600	0.310	<0.01**	0.25	0.385	0.031	<0.01**	<0.05*
Algan et al. 1996	Prostate	DU145	0.536	0.540	0.608	0.99	0.649	0.525	<0.01**	<0.05*	0.299	0.045	<0.01**	<0.05*
	Prostate	PC3	0.658	0.659	0.845	1.00	0.802	0.768	<0.01**	<0.01**	0.245	0.074	<0.01**	<0.01**
	Prostate	TSU	0.323	0.654	0.946	0.49	0.597	0.975	<0.01**	<0.01**	0.081	0.052	0.07	<0.01**
DeWeese et al. 1998	Prostate	DU145	0.355	0.424	0.733	0.84	0.474	0.692	<0.01**	<0.05*	0.189	0.022	<0.01**	<0.01**
	Prostate	LNCaP	0.146	1.091	0.002	0.13	0.894	0.403	<0.01**	<0.05*	0.527	0.069	<0.01**	<0.05*
	Prostate	PPC1	0.485	0.746	0.974	0.65	0.751	0.973	<0.01**	<0.01**	0.162	0.064	<0.01**	<0.01**
	Prostate	PC3	0.210	0.756	1.000	0.28	0.585	1.000	<0.01**	<0.01**	0.107	0.041	<0.05*	<0.01**
	Prostate	TSU-Pr1	0.000	0.897	0.448	0.00	0.607	0.701	<0.01**	<0.01**	0.254	0.033	<0.05*	<0.05*
Leith et al. 1993	Prostate	PC3	0.200	1.134	0.305	0.18	0.890	0.543	<0.01**	<0.01**	0.414	0.079	<0.01**	<0.01**
	Prostate	DU145	0.414	0.623	0.817	0.66	0.632	0.811	<0.01**	<0.01**	0.158	0.052	<0.01**	<0.01**
Suzuki et al. 1997	Embryo	HE20	0.329	1.409	1.000	0.23	1.049	1.000	<0.01**	<0.01**	0.000	0.211	1.00	<0.01**
Tsuboi et al. 1998	Glioma	A172	0.673	0.771	0.705	0.87	0.877	0.653	<0.01**	<0.01**	0.311	0.091	<0.01**	<0.01**
	Fibroblast	NB1RGB	0.598	0.598	0.499	1.00	0.713	0.399	<0.01**	<0.01**	0.389	0.052	<0.01**	<0.05*
	Medulloblastoma	ONS76	0.479	0.692	0.845	0.69	0.714	0.835	<0.01**	<0.01**	0.196	0.058	<0.01**	<0.01**
	Glioma	TK1	0.170	0.735	1.000	0.23	0.550	1.000	<0.01**	<0.01**	0.033	0.048	0.32	<0.01**
	Glioma	U251MG	0.231	0.759	1.000	0.30	0.597	1.000	<0.01**	5.85	0.018	0.059	0.31	<0.01**
Tsuchida et al. 1998	Glioma	A172	0.619	0.620	0.474	1.00	0.739	0.376	<0.01**	<0.01**	0.401	0.061	<0.01**	<0.01**
	Glioma	TK1	0.010	0.803	0.868	0.01	0.556	0.990	<0.01**	<0.01**	0.058	0.047	0.06	<0.01**
Kamlah et al. 2011	Lung	A594	0.425	0.425	0.403	1.00	0.491	0.255	<0.01**	<0.01**	0.296	0.028	<0.01**	<0.01**
Furusawa et al. 2000	Salivary gland	HSG	0.591	0.727	0.752	0.81	0.803	0.718	<0.01**	<0.01**	0.293	0.065	<0.01**	<0.01**
	Kidney	T1	0.410	0.562	0.840	0.73	0.592	0.820	<0.01**	<0.01**	0.219	0.031	<0.01**	<0.01**

Table 1 continued

Author/ref.	Cell type	Cell line	Fit to Eq. 7			$\varepsilon = p/q$	Fit to Eq. 9		p (q)	p (R)	Fit to LQ model			p (β)
			p	q	R		q	R			α	β	p (α)	
Chapman et al. 1978	Kidney	T1	0.320	0.561	0.965	0.57	0.538	0.981	<0.01**	<0.01**	0.097	0.037	<0.01**	<0.01**
Stenerlöw et al. 1995	Thyroid	HTh7	0.538	0.539	0.545	1.00	0.651	0.468	<0.01**	0.07	0.336	0.041	<0.01**	<0.01**
	Melanoma	IGR	0.344	0.771	1.000	0.45	0.673	1.000	<0.01**	<0.05*	0.077	0.062	0.35	<0.01**
	Colon	LS-174T	0.376	0.377	0.000	1.00	0.475	0.000	0.70	1.00	0.550	0.000	<0.01**	1.00
	Glioma	U-343MG	0.412	0.691	0.987	0.60	0.673	0.997	<0.01**	<0.05*	0.113	0.058	0.12	<0.05*
Persson et al. 2002	Melanoma	AA	0.347	0.520	0.960	0.67	0.529	0.955	<0.01**	<0.01**	0.054	0.046	<0.05*	<0.01**
Ito et al. 2006	Leukemia	HL-60	0.403	1.000	1.000	0.40	0.849	1.000	<0.01**	<0.05*	0.025	0.120	0.82	0.05

The fit of the unique solution of Eq. 9 is represented by the parameters p and q, and the fit to the LQ formalism by α and β. Single and double asterisks represent a statistical significant result for $p < 0.05$ and $p < 0.01$, respectively

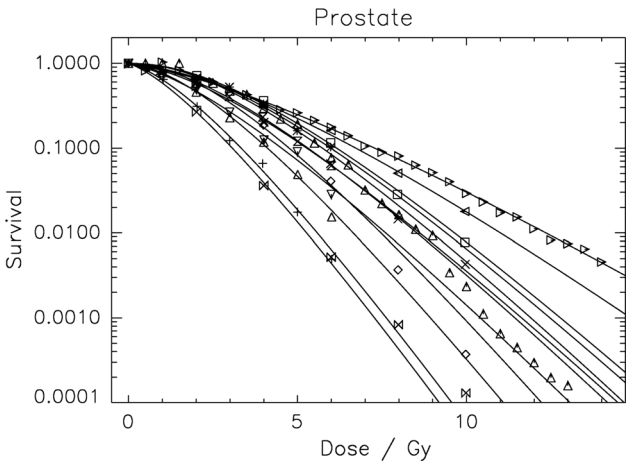

Fig. 2 Plot of the experimental survival data from prostate cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

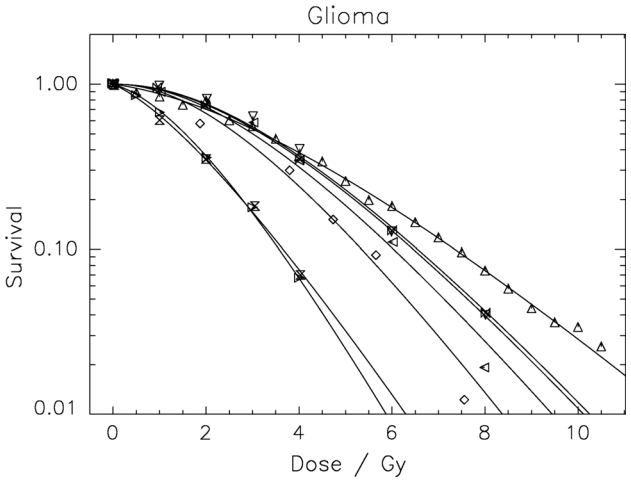

Fig. 3 Plot of the experimental survival data from Glioma cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

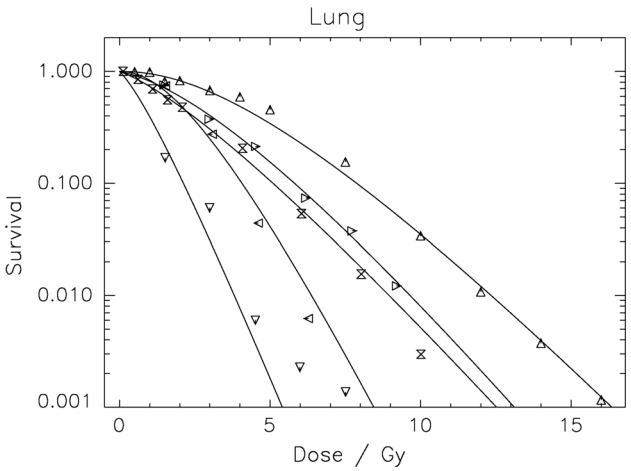

Fig. 4 Plot of the experimental survival data from lung cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

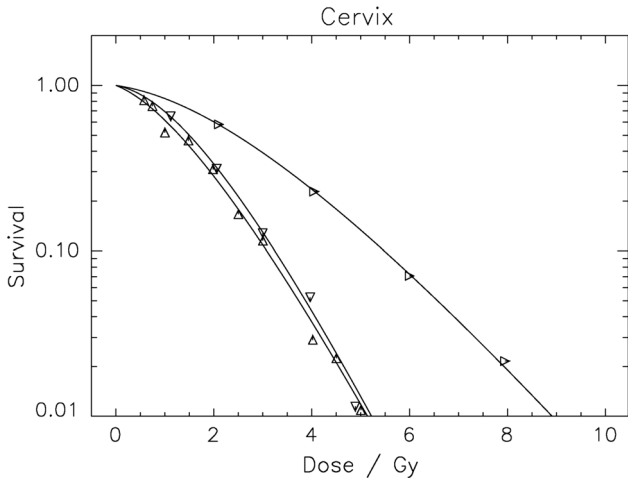

Fig. 5 Plot of the experimental survival data from cervix cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

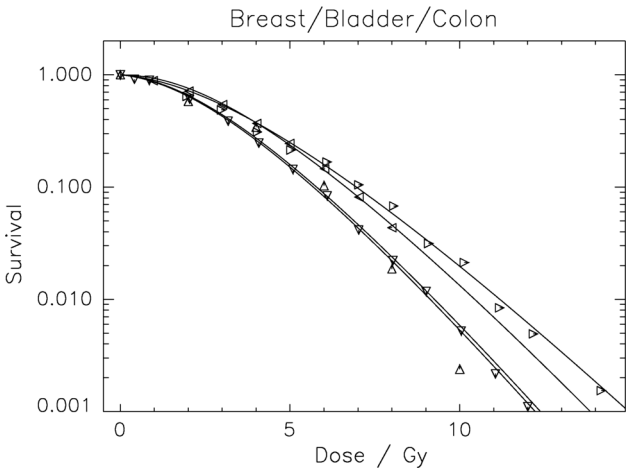

Fig. 7 Plot of the experimental survival data from breast, bladder, and colon cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

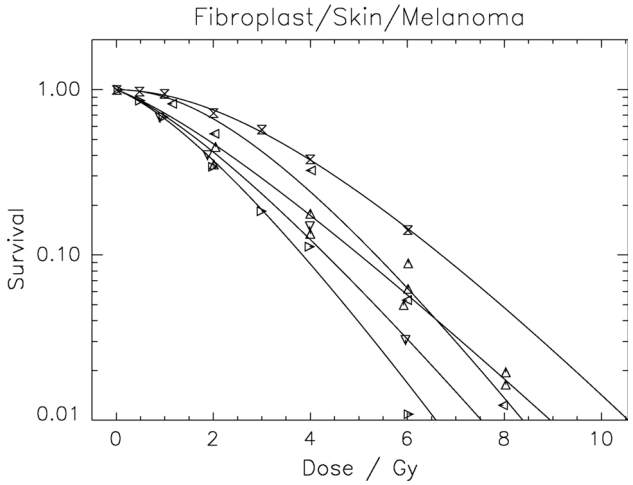

Fig. 6 Plot of the experimental survival data from fibroblast, skin, and melanoma cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

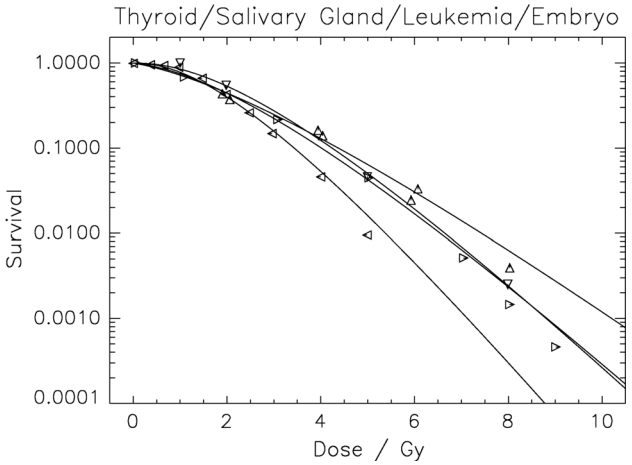

Fig. 8 Plot of the experimental survival data from thyroid, salivary gland, leukemia, and embryonal cell lines. The fits of the unique solution (Eq. 9) are shown as the *solid lines*

which is proportional to the ratio of the OTE and TTE probabilities should be independent of cell type, if cells with similar architecture of the basic chromatin organization are considered, however, will depend on radiation quality. The spatial distribution of energy deposition changes with changing LET, and thus, it would impact the OTE and TTE probabilities. It can be assumed that as higher the LET as lower the fraction of surviving TTEs. Thus, the p/q ratio is increased for increasing LET, resulting in cell survival curves with smaller shoulders. Therefore, the parameter q will depend on radiation quality as well as on cell type.

A second advantage of the presented model is that the predicted intrinsic shape of cell survival represents the characteristics of experimentally obtained cell survival curves that are, as mentioned above, exponential cell survival at high dose and a finite gradient of cell survival at vanishing dose.

One limitation of this work is the application of the model to cell survival curves that were obtained with high dose rates (0.7–2.0 Gy/min). However, radiotherapy dose rates in organs at risk can be lower. Therefore, the model in its current form is not likely applicable to the estimation of tolerance doses in radiotherapy. Further work is needed to include also the variation in cell survival with dose rate.

The solution for cell survival derived in this work (Eq. 9) is not modelling all biological effects that are related to cell death. There is still a lack of understanding of effects, as, for example, induced repair, low-dose hypersensitivity, and/or cell-cycle-dependent differences.

However, we believe that the cell survival model developed in this work can be superior to the LQ model for predicting isoeffects at high dose.

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