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Comparison of *in vitro* and *in vivo* α/β ratios for prostate cancer

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Abstract

Parallel *in vitro* and *in vivo* studies provide insight into the relationship between clinical response and intrinsic cellular radiosensitivity and may aid in the development of predictive assays. Compilations of radiosensitivity parameters from *in vitro* experiments can also be used to examine the potential effectiveness of alternative or new treatment plan designs until enough clinical data become available to directly estimate the requisite radiosensitivity parameters. In this work, survival data for six prostate cancer cell lines (ten datasets total) have been extracted from the literature and re-analysed using the linear-quadratic (LQ) survival model. The paired bootstrap technique for regression is used to compute 95% confidence intervals for the estimated radiosensitivity parameters. LQ radiosensitivity parameters derived from the *in vitro* data are then compared to radiosensitivity parameters derived from clinical data for prostate cancer. Estimates of α range from 0.09 to 0.35 Gy^{-1} (all cell lines), and the α/β ratio ranges from 1.09 to 6.29 Gy (all cell lines). Point estimates of the repair half-time (PPC-1, TSU-Pr1, PC-3 and DU-145 cell lines) range from 5.7 to 8.9 h (95% confidence interval from 0.26 h to 10.7 h). Differences in the radiosensitivity parameters determined from the data reported by different laboratories are as large as or larger than the differences in radiosensitivity parameters observed among the various prostate cell lines. The reported studies demonstrate that even seemingly small corrections for dose rate effects, such as those expected in high dose rate (HDR) experiments, can sometimes have a significant impact on estimates of α and α/β. By neglecting dose rate effects in the analysis of HDR experiments, estimates of the α/β ratio may be too high by factors as large as 1.3 to 6.2. The half-time for repair derived from

the *in vitro* experiments appears significantly larger (slower repair rate) than estimates derived from the clinical data. However, the prostate radiosensitivity parameters α and α/β may be approximately the same *in vitro* and *in vivo*. Most of the *in vitro* data are consistent with an α/β ratio for prostate cancer less than 3 or 4 Gy.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Prostate cancer is the most commonly occurring cancer in American males. The American Cancer Society estimates that approximately 230 110 new cases of prostate cancer will be diagnosed in the United States in the year 2004.[6] Early stages of prostate carcinoma are typically treated with surgical excision or with radiation therapy. Radiation therapy has shown success for the treatment of prostate carcinoma (Leibel *et al* 1994, Forman *et al* 1996, Freedman *et al* 1996). Common radiation therapy modalities include external beam radiation therapy (EBRT), low dose rate (LDR) brachytherapy, a combination of EBRT and LDR or high dose rate (HDR) brachytherapy boost. However, prescribed doses for these radiation treatment modalities have been developed empirically and alternative treatment plan designs may provide superior local tumour control or help minimize normal tissue complications (e.g., see Wang and Li (2003)).

Efforts to develop biologically optimal treatments are hampered by the lack of accurate radiosensitivity parameters, or distributions of parameters, for specific tumour sites and normal tissues. The ongoing debate about the most appropriate radiosensitivity parameters for prostate cancer illustrates well the challenges associated with the estimation of biological parameters. Brenner and Hall (1999) analysed the brachytherapy data of Stock *et al* (1998) and the EBRT data of Hanks *et al* (1997) and estimated the α/β ratio for prostate carcinoma at 1.5 Gy. This α/β ratio is much smaller than the 10 Gy value expected for most tumours (Thames *et al* 1990). Updated analyses of the available clinical data by Wang *et al* (2003a, 2003c), Kal and Van Gellekom (2003), Fowler *et al* (2001) and Brenner *et al* (2002) all suggest that the α/β ratio for prostate cancer is less than 3 or 4 Gy. However, Nahum *et al* (2003) conclude that tumour hypoxia and inter-patient variability in radiosensitivity parameters have a substantial impact on the estimates of the α/β ratio for prostate cancer. Nahum *et al* (2003) report that the α/β ratios for well-oxygenated and hypoxic prostate cancer cells are 8.5 and 15.5 Gy, respectively.

Several studies suggest that *in vitro* and *in vivo* radiosensitivity parameters may be correlated (Malaise *et al* 1986, Geara *et al* 1993, Oppitz *et al* 2001, Haikonen *et al* 2003). For skin fibroblasts, measurements of *in vitro* radiosensitivity were found to be related to the maximum grade of late skin effects (Geara *et al* 1993, Burnet *et al* 1994, Johansen *et al* 1994, 1996). However, the maximum grade of acute skin effects showed little correlation with *in vitro* radiosensitivity indicators (Geara *et al* 1993, Burnet *et al* 1994, Brock *et al* 1995, Johansen *et al* 1996, Begg *et al* 1993, Rudat *et al* 1997). The sometimes inconsistent correlations among *in vitro* radiosensitivity indicators and *in vivo* effects may be the result of small patient sample sizes, the lack of reliable radiosensitivity indicators (e.g., α, SF_2 and D_o), or the uncertain relationship among the *in vitro* radiosensitivity indicators and the *in vivo* endpoint of interest. Regardless, additional parallel studies of *in vitro* and

[6] Cancer Facts & Figures, 2004. American Cancer Society, Inc. 2004. Atlanta, GA.

in vivo radiosensitivity have the potential to aid ongoing efforts to develop predictive assays (Oppitz *et al* 2001, Haikonen *et al* 2003, Mariano Ruiz de Almodovar *et al* 2002) and may provide useful information to assess the biological plausibility of parameters derived from the clinical data. Compilations of *in vitro* radiosensitivity parameters can also be used to examine the potential effectiveness of new and alternative treatment plan designs until sufficient clinical data become available to directly estimate the requisite radiosensitivity parameters.

A number of published studies (Leith *et al* 1993, Algan *et al* 1996, Deweese *et al* 1998) report radiosensitivity parameters for prostate cancer cell lines. Some studies report survival data for HDR experiments while others report survival data for both LDR and HDR experiments. None of the original studies corrected for dose rate effects when analysing the measured data. In this work, radiosensitivity parameters determined from *in vitro* data for six prostate cancer cell lines (ten datasets total) are compiled, carefully re-analysed and compared to radiosensitivity parameters derived from the clinical data by Wang *et al* (2003a, 2003c), Kal and Van Gellekom (2003), Brenner and Hall (1999), Fowler *et al* (2001) and Brenner *et al* (2002). The goal is to gain insight into the possible relationship between *in vitro* and *in vivo* radiosensitivity parameters for prostate cancer. The *in vitro* data are also used to point out some additional, often overlooked, factors that can have a significant impact on the estimation of LQ radiosensitivity parameters. For example, accurate estimates of α and the α/β ratio cannot be determined using only HDR survival data (i.e., the exposure conditions most relevant to EBRT and IMRT). Instead, data for several doses and dose rates (or split-dose exposures) are required to determine accurate estimates of LQ radiosensitivity parameters. Similar issues also arise in the analysis of clinical data (Wang *et al* 2003c). Several studies illustrating the potential significance of the uncertainties that can arise when only HDR survival data are used to estimate radiosensitivity parameters are reported.

2. Methods and materials

2.1. Linear quadratic survival model

The mechanistic basis for the LQ survival model has been extensively reviewed in the literature (Sachs *et al* 1997, Brenner *et al* 1998, Guerrero *et al* 2002). In the limit of small doses and dose rates, the LQ can be derived from the lethal and potentially lethal (LPL) model (Curtis 1986) and the repair–misrepair (RMR) model (Tobias 1985) using the perturbation theory and other methods (Curtis 1986, Sachs *et al* 1997). The LPL and RMR models (and hence the LQ model) are broadly consistent with the breakage and reunion theory of chromosome aberration formation (reviewed in Sachs *et al* (1997), Hlatky *et al* (2002)). In the LQ, the fraction, S, of cells that survive absorbed dose D is given by

$$S = \exp[-D(\alpha + \beta G D)]. \tag{1}$$

As a first approximation, the quantity $D\,(\alpha + \beta GD)$ may be interpreted as the expected number of lethal point mutations and chromosome aberrations per cell. Lethal residual damage (unrejoined breaks) may also contribute to the αD term (see review by Chapman (2003)). The Lea–Catcheside dose-protraction factor G is given by (Sachs *et al* 1997)

$$G = \frac{2}{D^2}\int_{-\infty}^{\infty} \mathrm{d}t\ \dot{D}(t) \int_{-\infty}^{t} \mathrm{d}t'\ \dot{D}(t')\,\mathrm{e}^{-\lambda(t-t')}. \tag{2}$$

The quantity $\dot{D}(t)$ is the instantaneous absorbed dose rate (Gy h^{-1}) at time t. This dose rate function captures the temporal pattern of radiation delivery in its entirety. That is, equation (2) can be used, for example, to estimate the effects of protracting a single dose of radiation delivered at a constant dose rate as well as the protraction effects arising in split-dose and

Table 1. Summary of cell culture conditions for experimental colony survival assays. Cells were trypsinized and plated immediately in fresh growth media post-irradiation.

	Culture conditions				Irradiation conditions	
Experiment	Containment	Cell density	Growth medium*	Environment	Radiation type	Dose rate(s) (Gy h^{-1})
Deweese *et al* (1998)	Culture flasks	Subconfluent culture	RPMI 1640, 10% FBS	37 °C	^{137}Cs-0.667 MeV γ	0.25 and 60
Algan *et al* (1996)	Stirred suspension	60–80% confluence	DMEM/F-12K, 10% FBS, 1% P/S, 1% glutamine	5% CO_2, 37 °C	^{137}Cs-0.667 MeV γ	84
Leith *et al* (1993)	Culture flask	Exponential growth	RPMI 1640, 10% FBS, 1% sodium bicarbonate†	5% CO_2, 37 °C	250 kVp x-rays	60

* FBS, DMEM and P/S denote fetal bovine serum, Dulbecco's modified Eagle's medium and penicillin/streptomycin antibiotic, respectively.
† The growth medium used in the experiments of Leith *et al* (1993) also contained 1% antipleuropneumonia-like organism agent, 1% 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer and 0.04% gentamycin.

multi-fraction irradiation schemes. The biophysical interpretation of equation (2) is that a potentially lethal lesion, presumably the double strand break (DSB), is created at time t' and, if not repaired, may interact in pairwise fashion with a second lesion produced at time t (Sachs and Brenner 1998). The rate of damage repair is characterized by the rate constant λ or, alternatively, the effective half-time for repair $\tau \equiv \ln 2/\lambda$.

For a single dose of radiation delivered at constant dose rate, equation (2) reduces to

$$G(\lambda, T) = \left[\frac{2}{(\lambda T)^2}\right][e^{-\lambda T} + \lambda T - 1]. \tag{3}$$

The dose delivery time T equals $D/\dot{D}$. Even for the high dose rates, dose protraction effects may have a significant impact on cell killing and, ultimately, treatment effectiveness (e.g., see Wang *et al* (2003d)).

2.2. In vitro datasets for prostate cell lines

In vitro survival data for six prostate cell lines have been extracted from the literature: LNCaP (Deweese *et al* 1998), PPC-1 (Deweese *et al* 1998), TSU (Algan *et al* 1996), TSU-Pr1 (Deweese *et al* 1998), DU-145 (Deweese *et al* 1998, Algan *et al* 1996, Leith *et al* 1993) and PC-3 (Deweese *et al* 1998, Algan *et al* 1996, Leith *et al* 1993)[7]. Cell culture and irradiation conditions for each experiment are found in table 1. All cells were actively dividing and were plated immediately in fresh growth media post-irradiation. The Biosoft® Ungraph software was used to estimate the mean surviving fraction as a function of doses and dose rates from the published figures. The measured data were extracted from the published figures using several different data acquisition techniques, such as single point digitization and computing an average value from several points. Fits to the datasets generated using different data acquisition techniques give parameter estimates that are usually accurate to within 2 or 3 significant digits (data not shown), i.e., any systematic errors introduced into the measured data through the digitization process are nominal.

[7] Cell survival data extracted from the figures in the original publications are available online at http://rh.healthsciences.purdue.edu/archive/.

2.3. Analysis of in vitro survival data

A standard approach to parameter estimation involves minimizing a positively weighted sum of the errors. This weighted sum of the errors, sometimes termed a cost or loss function or a figure of merit, can be formulated in several different ways, depending on varying assumptions about the underlying probability model. The mathematical form of the loss function may impact on the estimation of parameters, on confidence intervals and on model inference. The impact that the choice of loss function has on parameter estimation is specific to the endpoint of interest and to the details of the mathematical model. The parameters of interest in the LQ survival formula are: α, β, and the half-time for repair τ.

Let X_i denote the ith estimate of the surviving fraction and $P_i(\mathbf{x})$ be the model-predicted surviving fraction for the same exposure conditions where $\mathbf{x}$ denotes the set of LQ parameters that can be adjusted to minimize a prescribed loss function (i.e., α, β, τ or $\lambda = \ln 2/\tau$). All parameter estimates reported in this work were estimated using the loss function

$$\chi^2 = \sum_{i=1}^{N} \left[\frac{P_i(\mathbf{x}) - X_i}{P_i(\mathbf{x})} \right]^2. \tag{4}$$

Here N is the total number of data points (experiments). Equation (4) is a weighted quadratic loss function which reflects the assumption that the variance of the surviving fraction is proportional to the squared or absolute predicted value. Loss functions that account for the estimated variance in the measured data (e.g., the weighted least-squares approach, see Press *et al* (1992)) generally result in estimates that are less variable.

The measured data reported in the publications considered did not include any information to estimate the variance associated with the measured data. Consequently, we used the paired bootstrap technique for regression (Efron 1979) to compute 95% confidence intervals for the estimated radiosensitivity parameters. Point estimates of the LQ radiosensitivity parameters were obtained by minimizing equation (4) using the quasi-Newton, nonlinear optimization algorithm implemented in the Microsoft® Excel software. To minimize the chance that the optimization algorithm converges to a sub-optimal (local) solution instead of a global optimum, the quasi-Newton algorithm was started using several initial estimates of the LQ radiosensitivity parameters. LQ radiosensitivity parameters were constrained to non-negative values when necessary (i.e., when negative parameter estimates were obtained).

3. Results

Because of the nonlinear nature of the LQ survival model, estimates of the radiosensitivity parameters α, α/β and τ are very sensitive to the details of the data analysis methodology and to the availability of measured data for several different dose rates (or alternatively, data for single-dose, split-dose and other multi-fraction irradiation schemes). To illustrate the potential significance of these issues, we used the LQ model to analyse survival data for several prostate carcinoma cell lines. Some of these *in vitro* datasets only include survival data for HDR exposure conditions while other datasets include survival data for both LDR and HDR exposure conditions. The effects of assumptions regarding the value of the dose protraction factor G have been investigated by fitting the survival data to the LQ model for two cases: [1] using the general form of G (refer to equation (3)) and [2] assuming G is unity for the case of HDR irradiation.

The results are organized as follows. First, the results of several studies investigating how the details of the data analysis methodology impact on parameter estimates are presented. Results illustrating the need for survival data for several different dose rates are also presented.

Table 2. Estimated range of LQ radiosensitivity parameters that can be derived from the HDR survival data for all prostate cell lines. G is computed using the indicated value of τ for α/β in columns 2 and 3.

	α/β (Gy)		
Cell lines	$\tau = 0.1$ h	$\tau = 6$ h	$G = 1$
LNCaP (Deweese *et al* 1998)	27.64	49.68	50.21
PPC-1 (Deweese *et al* 1998)	0.43	2.69	2.75
TSU-Pr1 (Deweese *et al* 1998)	4.96	10.29	10.42
DU-145 (Deweese *et al* 1998)	4.08	8.71	8.83
DU-145 (Algan *et al* 1996)	4.36	5.74	5.77
DU-145 (Leith *et al* 1993)	1.85	3.19	3.21
PC-3 (Deweese *et al* 1998)	0.90	3.40	3.46
PC-3 (Algan *et al* 1996)	2.14	3.12	3.14
PC-3 (Leith *et al* 1993)	3.17	4.96	5.00
TSU (Algan *et al* 1996)	1.08	1.82	1.83

The significance of the uncertainties associated with parameter estimates determined from the HDR survival data is examined for a clinically relevant 2 Gy dose (SF_2). Best estimate radiosensitivity parameters have been derived using a consistent data analysis methodology and are reported for the available *in vitro* prostate carcinoma datasets. Estimates of the *in vitro* radiosensitivity parameters are then compared to radiosensitivity parameters that have been derived from the clinical data for the treatment of prostate cancer.

3.1. Re-analysis of in vitro survival data

Table 2 shows the estimated range of LQ radiosensitivity parameters that can be derived from the HDR survival data for the prostate carcinoma cell lines. For all cell lines, setting the protraction factor, G, to unity *a priori* results in the maximum estimate of the α/β ratio. The estimated value of the α/β ratio tends to decrease, sometimes substantially, when the protraction factor is estimated using representative repair half-times from 0.1 to 6 h. For repair half-times in the range of 0.1 to 6 h, the estimates of the α/β ratio may be as much as 1.3 to 6.2 times lower than the corresponding values determined with G set *a priori* to unity. The estimated α/β ratio increases towards the maximum as the half-time for repair increases because G approaches unity as the product $T\lambda = T \ln 2/\tau$ becomes small (refer to equation 3).

Figure 1 shows the PC-3 cell surviving fraction (Deweese *et al* 1998) as a function of absorbed dose for two different dose rates (0.25 and 60 Gy h^{-1}). Solid lines show the surviving fraction predicted using parameters estimated from a simultaneous fit to both the LDR and HDR survival data ($\alpha = 0.145$ Gy^{-1}, $\alpha/\beta = 4.11$ Gy, $\tau = 6.59$ h). Dashed lines show the surviving fractions predicted using radiosensitivity parameters determined from the HDR data with G set *a priori* to unity ($\alpha = 0.128$ Gy^{-1}, $\alpha/\beta = 3.46$ Gy). As expected, the solid and dashed lines are both in good agreement with the measured data for the HDR exposure conditions. The dotted lines show the surviving fraction predicted for the LDR exposure conditions using three representative repair half-times (0.1, 2 and 6.59 h) and the radiosensitivity parameters determined from the HDR data (G set *a priori* to unity). To obtain

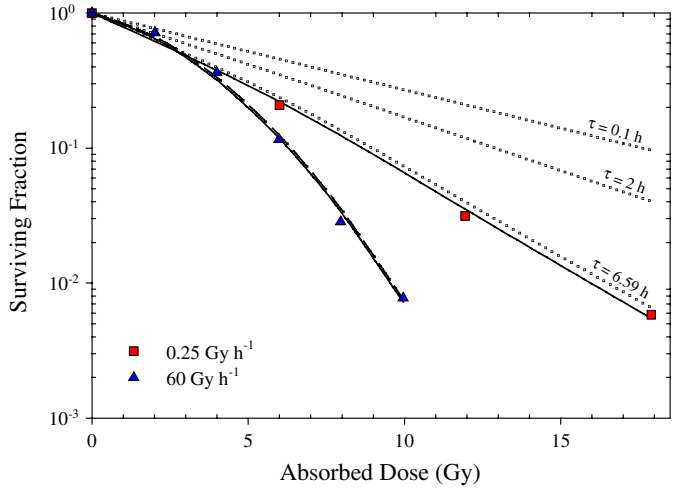

Figure 1. Comparison of measured and predicted PC-3 surviving fractions using different parameter estimation strategies. Measured data are from Deweese *et al* (1998). Solid lines: parameters derived from LDR and HDR survival data ($\alpha = 0.145$ Gy^{-1}, $\alpha/\beta = 4.11$ Gy, $\tau = 6.59$ h). Dashed line: parameters derived from HDR survival data with G set *a priori* to unity ($\alpha = 0.128$ Gy^{-1} and $\alpha/\beta = 3.46$ Gy). Dotted lines: G is computed using three representative repair half-times (α and α/β same as dashed lines).

accurate estimates of the surviving fraction for LDR exposure conditions, an accurate estimate of the repair half-time τ is clearly needed.

Figure 2 shows the fraction of PC-3 cells that are expected to survive a 2 Gy dose (SF_2) as a function of dose rate. The solid line illustrates the expected SF_2 for a range of dose rates derived from a simultaneous fit to both the LDR and HDR survival data ($\alpha = 0.145$ Gy^{-1}, $\alpha/\beta = 4.105$ Gy, $\tau = 6.59$ h). Dotted lines show the expected SF_2 when the radiosensitivity parameters are estimated using the HDR survival data and three (assumed) repair half-times: 0.1 h ($\alpha = 0.056$ Gy^{-1}, $\alpha/\beta = 0.90$ Gy), 2 h ($\alpha = 0.125$ Gy^{-1}, $\alpha/\beta = 3.28$ Gy) and 6.59 h ($\alpha = 0.127$ Gy^{-1}, $\alpha/\beta = 3.40$ Gy). The $G = 1$ ($SF_2 = 0.65$) and $G = 0$ ($SF_2 = 0.75$) asymptotes are the high and low dose rate surviving fractions, respectively. Within the 3–30 Gy h^{-1} effective dose rate range (the range of dose rates most relevant to step-and-shoot IMRT, e.g. 2 Gy delivered in 20 min is equivalent to an average dose rate of 6 Gy h^{-1}), estimates of the surviving fraction may differ by as much as 2–17%.

Table 3 reports the best estimates of the LQ radiosensitivity parameters for all of the *in vitro* prostate carcinoma cell lines. For published datasets that include survival data for several dose rates, estimates of all three radiosensitivity parameters are reported (α, β, τ). For datasets that only report survival data for HDR exposure conditions, the reported best estimate parameters are based on a representative 2 h repair half-time (i.e., G is computed for the specified HDR exposure using $\lambda = 0.3467$ h^{-1}). Lower and upper bounds on the α/β ratio for the parameters determined from the HDR survival data can be obtained from the data shown in table 2. For comparison, the estimates of α and α/β from the original publication are also reported. Differences among our best estimates and the originally reported parameter estimates can be attributed to differences in the data analysis methodology (e.g., choice of loss function) and to neglecting the effects of dose rate in HDR survival experiments. That is, the reported estimates of α and β are based on the assumption that the dose protraction factor G equals unity for HDR exposure conditions.

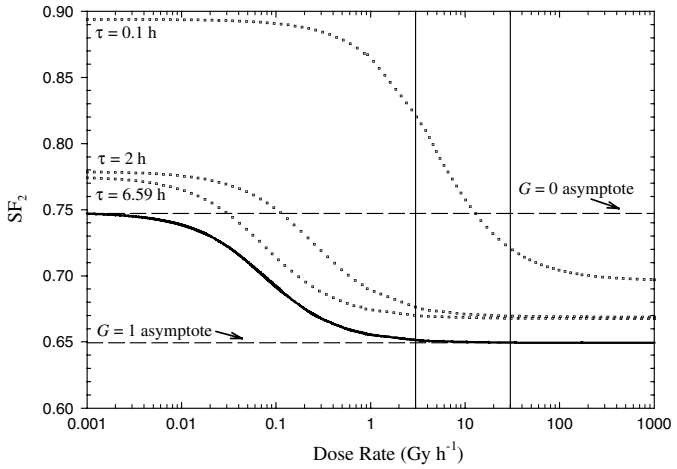

Figure 2. Fraction of the PC-3 prostate cells expected to survive a 2 Gy dose (SF_2) as a function of dose rate. Solid line: parameters derived from LDR and HDR survival data ($\alpha = 0.145$ Gy^{-1}, $\alpha/\beta = 4.105$ Gy, $\tau = 6.59$ h). Dotted lines: parameters determined from HDR survival data using three different repair half-times: 0.1 h ($\alpha = 0.056$ Gy^{-1}, $\alpha/\beta = 0.90$ Gy), 2 h ($\alpha = 0.125$ Gy^{-1}, $\alpha/\beta = 3.28$ Gy) and 6.59 h ($\alpha = 0.127$ Gy^{-1}, $\alpha/\beta = 3.40$ Gy). Vertical solid lines at dose rates of 3 Gy h^{-1} and 30 Gy h^{-1} represent the effective dose rate that is most relevant to IMRT (see Wang *et al* (2003) for additional discussion). All radiosensitivity parameters fit the HDR survival data of Deweese *et al* (1998) equally well.

3.2. Comparison of in vitro and in vivo radiosensitivity parameters

Figure 3 shows a comparison of LQ radiosensitivity parameters derived from the available *in vitro* and *in vivo* (clinical) data. Solid lines indicate the range of LQ radiosensitivity parameters that can be derived from the *in vitro* survival data for HDR exposure conditions (half-times for repair in the range of 0.1–6 h). An increase in the α radiosensitivity parameter corresponds to an increase in the repair half-time τ. All prostate cell lines exhibit a similar trend, i.e., an increase in β corresponds to a decrease in α. Open symbols show the estimated best-fit radiosensitivity parameters derived from *in vitro* survival data for low and high dose rates (Deweese *et al* 1998). Clinically determined α/β values (Brenner and Hall 1999, Fowler *et al* 2001, Brenner *et al* 2002, Wang *et al* 2003a, 2003c, Kal and Van Gellekom 2003) are shown as solid symbols.

The *in vitro* datasets indicate that α is in the range from about 0.09 Gy^{-1} (TSU) to 0.4 Gy^{-1} (PC-3) and the α/β ratio is in the range from 1.1 Gy to 6.3 Gy. However, the radiosensitivity parameters for the LNCaP cell line appear somewhat atypical compared to the other cell lines (see figure 3) because the estimated repair half-time is only 0.66 min. If the parameter estimates of the LNCaP cell line (Deweese *et al* 1998) are excluded, the *in vitro* data suggest an α/β ratio in the range from 1.8 Gy to 6.3 Gy. For comparison, Wang *et al* (2003a) report that $\alpha = 0.15$ Gy^{-1} and the α/β ratio is 3.1 Gy. Both of these radiosensitivity parameters are well within the range observed in the *in vitro* datasets. In contrast, the estimates of α and β obtained by Brenner and Hall (1999), Fowler *et al* (2001) and Brenner *et al* (2002) are at the low end of the range observed in the *in vitro* datasets (see figure 3). Overall, the data shown in figure 3 indicate that the radiosensitivity parameters determined from the available *in vitro* data are more consistent with parameters derived from clinical data by Wang *et al* (2003a, 2003c) and Kal and Van Gellekom (2003). The radiosensitivity parameters reported by Brenner and Hall (1999), Fowler *et al* (2001) and Brenner *et al* (2002) appear to be less

Table 3. Best estimates of LQ parameters derived from the reanalysis of published prostate carcinoma survival data. For published datasets that include survival data for multiple dose rates, three-parameter (α, β, τ) fits are shown (G is computed from τ and the dose and dose rate information).

		α/β (Gy)		τ (h)		Literature reported	
Cell lines	α (Gy^{-1})	Point estimates	95% CI	Point estimates	95% CI	α (Gy^{-1})	α/β (Gy)
LNCaP (Deweese *et al* 1998)	0.351	1.086	(1.056, 1.361)	0.011	(0.011, 0.014)	0.29	22.30
PPC-1 (Deweese *et al* 1998)	0.160	2.485	(1.892, 3.051)	8.405	(7.681, 8.704)	0.1	3.85
TSU-Pr1 (Deweese *et al* 1998)	0.182	4.723	(2.422, 10.688)	8.890	(0.260, 10.690)	0.115	7.667
DU-145 (Deweese *et al* 1998)	0.159	6.287	(4.091, 9.743)	5.674	(2.705, 7.125)	0.099	11.000
DU-145 (Algan *et al* 1996)*	0.278	5.706	(2.902, 15.511)	–	–	0.313	6.521
DU-145 (Leith *et al* 1993)*	0.161	3.113	(2.329, 3.361)	–	–	0.155	2.975
PC-3 (Deweese *et al* 1998)	0.145	4.105	(2.513, 5.716)	6.590	(5.337, 7.954)	0.064	3.765
PC-3 (Algan *et al* 1996)*	0.235	3.088	(2.218, 4.150)	–	–	0.241	3.493
PC-3 (Leith *et al* 1993)*	0.398	4.927	(3.167, 7.509)	–	–	0.487	8.855
TSU (Algan *et al* 1996)*	0.090	1.795	(0.646, 3.419)	–	–	0.062	1.240

The $*$ indicates that there are insufficient measured data available to estimate the repair half-time. For these datasets, the reported estimates are based on computing G using a 2 h repair half-time. For comparison, the estimates of α and α/β from the original publication are also reported. The paired bootstrap technique for regression (Efron 1979) was used to compute the 95% confidence intervals because experimental variances on the data points were not reported.

consistent with the available *in vitro* datasets, although some overlap in the estimates of α or β (but not both) may be possible.

4. Discussion

The dose protraction factor G plays an important role in the analysis of cell survival data, even survival data obtained in HDR experiments. As the data in table 2 illustrate, the estimates of the α/β ratio obtained with repair half-times from 0.1 to 6 h are lower, sometimes substantially lower, than the estimates obtained with the protraction factor set *a priori* to unity. The systematic error introduced into estimates for α/β may be a factor of 1.3 to 6.2 too high. These systematic errors arise because, for any finite dose rate, the irradiation time increases with increasing dose. As the irradiation time increases, the protraction factor decreases (refer to equation 3). For the HDR experiments listed in table 3, the possible range of protraction factors is: 0.71–0.99 (Deweese *et al* 1998), 0.85–0.99 (Algan *et al* 1996) and 0.80–0.99 (Leith *et al* 1993). These estimates are based on repair half-times from 0.1 to 6 h. Smaller values of G correspond to larger doses and smaller (faster) repair half-times. In terms of reaction-rate models such as the LPL, RMR and TLK (reviewed in Guerrero *et al* (2002), Sachs *et al* (1997)), an inverse relationship between α/β and the repair half-time implies that the rate

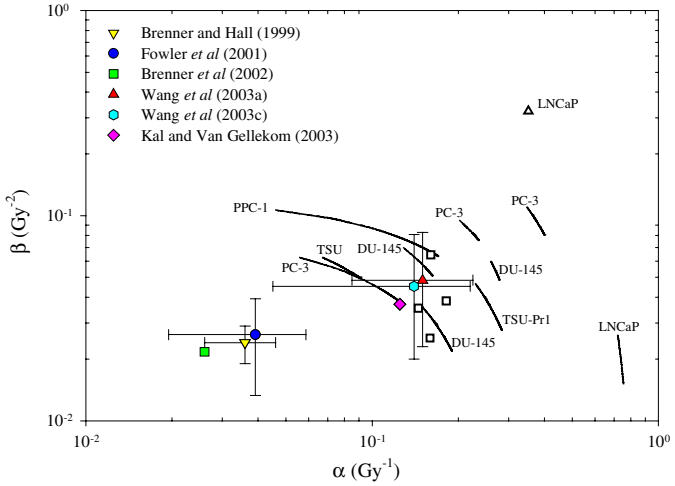

Figure 3. Comparison of *in vitro* and *in vivo* LQ radiosensitivity parameters for prostate carcinoma (Brenner and Hall 1999, Fowler *et al* 2001, Brenner *et al* 2002, Wang *et al* 2003a, 2003c, Kal and Van Gellekom 2003). Filled symbols indicate parameters derived from clinical data. Solid black lines indicate the range of LQ parameters that fit the available *in vitro* HDR survival data equally well (repair half-times from 0.1 to 6 h). Open symbols indicate parameters estimated from *in vitro* datasets (Deweese *et al* 1998, Algan *et al* 1996, Leith *et al* 1993) containing both LDR and HDR survival data (DU-145, PC-3, PPC-1, TSU-Pr1 and LNCaP). The open triangle, although derived from LDR and HDR survival data (LNCaP cells), is questionable because the estimated repair half-time is only 0.66 min. Error bars associated with the filled symbols indicate the estimated 95% CI 95% CIs for α and β are not reported by Brenner *et al* (2002) and Kal and Van Gellekom (2003).

of pairwise DSB interaction increases as the first-order DSB rejoining rate increases. A correlation between β and the repair half-time is known to exist (Brenner 1992), and a positive correlation between the values of α and β has also been reported (Peacock *et al* 1992). For the analysis of cell survival data, the assumption that $G = 1$ for all HDR experiments is an oversimplification of the LQ model which can produce systematic errors in the estimation of radiosensitivity parameters. Similar considerations may also apply to the assumption that $G = 0$ for LDR experiments.

As shown in table 3, the α/β ratio for DU-145 cells varies about two-fold from 3.1 to 6.3 Gy. For PC-3 cells, estimates of α/β vary by a factor of 1.6, i.e., from 3.1 to 4.9 Gy. The α/β ratio for the other cell lines (LNCaP, PPC-1, TSU-Pr1 and TSU) ranges from 1.1 to 4.7 Gy. The estimates of α range from 0.09 Gy^{-1} (TSU) to 0.40 Gy^{-1} (PC-3). Differences in the radiosensitivity parameters determined from data reported by different laboratories are as large as or larger than the differences in radiosensitivity parameters observed among the various prostate cell lines. This observation indicates that the details of the experimental protocol (see table 1) have as much impact on estimates of LQ parameters as any differences in the intrinsic radiosensitivity of the cell lines. A considerable amount of uncertainty in estimates of LQ radiosensitivity parameters can also arise because of the data analysis methodology and because the available measured data often do not include sufficient information to determine a unique value for α, β and τ (table 2). Estimates of radiosensitivity parameters are also sensitive to the range of doses used in the analysis. As an example, the analysis of the entire PC-3 dataset reported by Deweese *et al* (1998) gave values of 4.11 Gy and 6.59 h for α/β

and τ, respectively. When the survival data above 8 Gy are excluded from the analysis, α/β decreases to 1.46 Gy and τ increases to 12.33 h.

Figure 2 shows that the predicted SF_2 value for PC-3 cells can be sensitive to the details of the method used to estimate radiosensitivity parameters. Radiosensitivity parameters derived from both dose rates give a SF_2 of ∼65%, while the parameters determined from just the HDR data predict values of the SF_2 in the range from ∼ 67 to 82%, depending on the repair half-time and dose rate. These data suggest that the radiation treatment regimes that are optimized using radiosensitivity parameters derived from an analysis of HDR data with G set to unity may underestimate the true amount of cell killing. When differences in the SF_2 are compounded over 30 daily fractions, these systematic (data analysis) errors can become very large (i.e., the predicted levels of cell killing may differ by factors ranging from 2 to 10^3).

In practice, the estimates of the half-time for repair, τ, can only be obtained when survival data for several different exposure conditions are available. The estimated repair half-times for the DU-145 and PC-3 cell lines (Deweese *et al* 1998) are 5.7 h and 6.6 h, respectively. For the PPC-1 and TSU-Pr1 cell lines (Deweese *et al* 1998), the estimated repair half-times are 8.4 h and 8.9 h, respectively. The estimated repair half-time for the LNCaP cell line is 0.66 min. This very short repair half-time is an indication of the atypical nature of the LNCaP cell line when compared to the other prostate cell lines (see figure 3). With the exception of the LNCaP cell line, the *in vitro* data suggest that repair half-times greater than 5 or 6 h may be appropriate for prostate carcinoma.

Double strand breaks (DSBs), the putative potentially lethal lesion, are often rejoined with bi-phasic rejoining kinetics (Nelson *et al* 1990, Van Rongen *et al* 1993, Millar *et al* 1996, Kampinga *et al* 1997, Steel *et al* 1987, Stewart 2001). The fast rate of DSB rejoining is typically on the order of 0.1 to 0.5 h, whereas the slow DSB rejoining rate is typically greater than 4 to 6 h. The slow DSB rejoining rate may even be as long as 10 to 20 h for some cell lines (Nelson *et al* 1990, Stewart 2001, Guerrero *et al* 2002). The average half-time for repair that appears in the LQ model can be interpreted as an average of the fast and slow DSB rejoining rates (e.g., see table 1 in Guerrero *et al* (2002)). The observation that the average half-time for repair is greater than 5 or 6 h implies that the slow-rejoining DSBs are the ones that are responsible for most of the observed *in vitro* cell killing effects. For comparison to the *in vitro* repair half-times, an analysis of clinical data by Wang *et al* (2003a) and Fowler *et al* (2001) results in repair half-times of 0.27 h (standard CI from 0 to 1.5 h) and 1.9 h (95% CI from 1.4 to 2.9 h), respectively. Estimates of the half-time for repair obtained from the *in vitro* and clinical data appear significantly different, although the 95% CI for one of the DU-145 datasets (see table 3) does overlap with the 2.9 h upper 95% CI reported by Fowler *et al* (2001).

Figure 3 compares the estimates of radiosensitivity parameters derived from the *in vitro* and *in vivo* (clinical) data. Nahum *et al* (2003) have also compared *in vitro* and clinically derived radiosensitivity parameters. They report that the α/β ratios for well-oxygenated and hypoxic prostate cancer cells are 8.5 and 15.5 Gy, respectively. However, they made no attempt to correct for dose rate effects, and the radiosensitivity parameters for PC-3 cells (Leith *et al* 1993) are reported incorrectly in table 1 by Nahum *et al* (2003). As the results shown in tables 2 and 3 illustrate, corrections for dose rate effects can have a significant impact on estimates of LQ radiosensitivity parameters. Our re-analysis of the *in vitro* data suggests the α/β ratios reported by Nahum *et al* (2003) are too high. Overall, we find that the estimates of α and β derived from the *in vitro* data overlap with those derived from the clinical data by Wang *et al* (2003a, 2003c) and Kal and Van Gellekom (2003). The estimates of α obtained by Brenner and Hall (1999) and Fowler *et al* (2001) are at least a factor of two smaller than the smallest estimate of α obtained from the *in vitro* datasets (i.e., 0.039 Gy^{-1} compared to

0.09 Gy^{-1}). Their estimates of β are also at the low end of the range observed in the *in vitro* datasets (i.e., $\sim$0.035 Gy^{-2} compared to 0.03 to 0.08 Gy^{-2} for the *in vitro* datasets, excluding the atypical LNCaP cell line).

The observation that radiosensitivity parameters differ widely among laboratories even for the same cell line (table 3) demonstrates that the cell microenvironment has a major impact on radiation response, as expected. However, many other factors may also have a substantial impact on estimates of radiosensitivity parameters derived from *in vitro* and clinical data. A 10% uncertainty in the reported dose used to analyse the *in vitro* survival data translates to a 10% uncertainty in α/β and τ (data not shown). Studies by D'Souza *et al* (2004) suggest that extreme underdosing of a small portion of the tumour may result in a greater local tumour control than moderately underdosing a relatively large portion of the tumour and vice versa. This study suggests that the analysis of clinical outcomes from brachytherapy using the prescription dose (or other scalar dose quantities) instead of the full three-dimensional dose distribution may bias estimates of radiosensitivity parameters.

Carlone *et al* (2003a) suggest that prostate radiosensitivity parameters may change throughout the irradiation procedure due to reoxygenation and redistribution effects. These dynamic processes are most likely influenced by treatment fractionation (Carlone *et al* 2003a). Inter-patient variations in intrinsic radiosensitivity can have an effect on the estimation of both tumour control probabilities and normal tissue complication probabilities (Lindsay *et al* 2003). There is likely a range of radiosensitivity parameters that applies to a population of individuals as opposed to a unique value that can be accepted as the standard. However, Carlone *et al* (2003b) found that both homogenous (individual) and heterogeneous (population) tumour control models yield equivalent estimates of the α/β, while the homogeneous model overestimates the significance of α/β (i.e., the 95% CI from the heterogeneous model is much larger). Published analyses of clinical data (Brenner and Hall 1999, Fowler *et al* 2001, Brenner *et al* 2002, Wang *et al* 2003a, 2003c, Kal and Van Gellekom 2003) are generally premised on the idea that the radiosensitivity of prostate carcinoma can be characterized using a single average (effective) set of LQ parameters.

In view of the many potential reasons why radiosensitivity parameters derived from *in vitro* and clinical data might differ, it is all the more striking that combinations of values for α and β derived from the *in vitro* experiments overlap with those derived from clinical data by Wang *et al* (2003a, 2003c) and Kal and Van Gellekom (2003) but not those reported by Brenner and Hall (1999), Fowler *et al* (2001) and Brenner *et al* (2002) (figure 3). However, it is important to note that the confidence intervals for all of the *in vivo* α/β estimates overlap with each other. For example, the 95% confidence interval determined by Brenner *et al* (2002) for the α/β ratio is [0.03, 4.1] Gy, which includes the value of 3.1 Gy reported by Wang *et al* (2003a) as well as the Kal and Van Gellekom (2003) range of 3.1–3.9 Gy. The overlap among some of the *in vitro* and *in vivo* estimates for α and α/β suggests that the key aspects of intrinsic radiation sensitivity may be approximately the same *in vitro* and *in vivo*. However, the direct analysis of clinical data using *in vitro* radiosensitivity parameters can produce unreasonable estimates for the number of tumour clonogens (Roberts and Hendry 1998). Considerations such as these highlight the limitations of using *in vitro* radiosensitivity parameters to directly predict clinical outcomes.

5. Conclusions

Comparisons of radiosensitivity parameters derived from *in vitro* and clinical data can provide useful insights into the similarities and differences among key radiosensitivity parameters. The half-time for repair derived from the *in vitro* experiments appears significantly larger

(slower repair rate) than estimates derived from clinical data. However, our studies suggest that the prostate radiosensitivity parameters α and α/β may be approximately the same *in vitro* and *in vivo*. Although the 95% confidence interval on the *in vitro* α/β estimates includes one value as high as 15.5 Gy, the lower bound on the 95% confidence interval is between 0.65 and 4.1 Gy for all cell lines analysed. We conclude that the estimates of the α/β ratio derived from the *in vitro* and clinical data are consistent with prostate cancer cells having an α/β ratio less than about 3 or 4 Gy.

Estimates of the intrinsic radiosensitivity parameters (α, α/β and τ) derived from *in vitro* data could be significantly improved by using a wider range of doses and, especially, dose rates and by standardizing the data analysis methods and experimental procedures. Because of the nonlinear nature of the LQ, estimates of α and α/β can be sensitive to seemingly small corrections for dose rate (irradiation time) effects. By neglecting dose rate effects in the analysis of HDR experiments, estimates of the α/β ratio may be too high by factors as large as 1.3 to 6.2. Care should be exercised when using the LDR ($G = 0$) and HDR ($G = 1$) approximations to analyse survival data. The LDR approximation is valid when the irradiation time is much greater than the repair half-time, and the HDR approximation is valid when the irradiation time is much smaller than the repair half-time. It is important to note that, for any finite dose rate no matter how large, irradiation time must increase with increasing dose. As the irradiation time increases, the protraction factor decreases (i.e., the HDR approximation becomes questionable). These considerations also apply to the analysis of clinical data. For many radiation treatment modalities (e.g., step-and-shoot IMRT), the total time required to deliver a fraction ($\sim$10 to 30 min) is comparable to the repair half-times expected for many tumour cell lines, and dose protraction effects may not be negligible (e.g., see Wang *et al* (2003d)).

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