Reply to 'Comments on 'Comparison of *in vitro* and *in vivo* α/β ratios for prostate cancer' '

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The Editor,
Sir,

We thank Drs Daşu and Fowler for their positive remarks on our re-analysis of the *in vitro* data for prostate cancer and for their valuable contributions to the ongoing debate on the most appropriate radiosensitivity parameters derived from clinical data. A key objective of the Carlson *et al* (2004) paper was to examine whether or not the available *in vitro* data for prostate cancer cells are consistent with the low α/β ratios that have been recently derived from clinical data. In contrast to Nahum *et al* (2003), we found that the *in vitro* data do provide support for a low α/β, and we agree with Drs Daşu and Fowler that our findings have potentially important implications for the treatment of prostate cancer using hypofractionation. However, Drs Daşu and Fowler argue in their letter that α/β for prostate cancer *in vivo* is closer to 1–2 Gy rather than 3–4 Gy as reported by others (Wang *et al* 2003a, 2003b and Kal and Van Gellekom 2003), including three of us (JZW, MG, and XAL), and we would like to respond to their comments.

In vitro and in vivo radiosensitivity

In the Carlson *et al* (2004) paper, we re-analysed survival data for 10 *in vitro* prostate cancer cell lines. A major finding from our re-analysis of the published survival data indicates that even seemingly small corrections for dose rate effects can have a substantial impact on estimates of α/β derived from *in vitro* data. All of the point estimates for α are larger than 0.09 Gy^{-1}, and point estimates of α/β are larger than 3 Gy for seven out of 10 datasets (see table 3 in Carlson *et al* (2004)).

To facilitate comparisons between *in vitro* and *in vivo* radiosensitivity parameters, we have pooled all of the *in vitro* data and computed the geometric means and the corresponding standard deviations for α, β and α/β. The standard deviations are based on log-normally distributed radiosensitivity parameters (Brenner and Hall 1991, Wang *et al* 2005). The results of this analysis are shown in table 1. For comparison, the radiosensitivity parameters derived by Fowler *et al* (2001) and by Wang *et al* (2003a, 2003b) are also shown in table 1. Estimates of α and α/β reported by Brenner and Hall (1999) are the same as those reported by Fowler *et al* (2001). Estimates of α, β and α/β derived from the clinical data by Wang *et al* are well within the estimated standard confidence intervals (CI) for the *in vitro* parameters. The estimates for α, β and α/β reported by Fowler *et al* (2001) are outside of the standard CI. Estimates for α are even outside the estimated 95% CI (0.08, 0.59).

The inconsistencies between the *in vitro* and clinical estimates of Fowler *et al* (2001) (and Brenner and Hall 1999, Brenner *et al* 2002) can also be clearly seen in figure 3 of Carlson *et al* (2004). Although the 95% CIs for each individual parameter overlap, a two-dimensional plot of α versus β shows two distinct groupings of radiosensitivity parameters. The points that represent the *in vivo* estimates from Brenner and Hall (1999), Fowler et al (2001) and Brenner et al (2002) clearly lie outside the estimated range of *in vitro* values. On the other hand, despite the large variation of the *in vitro* data, estimates of α and β parameters derived by Wang *et al* (2003a, 2003b) and Kal and Van Gellekom (2003) show a significant overlap with the *in vitro* estimates.

Table 1. Comparison of LQ parameters derived from *in vitro* and *in vivo* studies.

LQ Parameters		α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)
In vitro	Mean[b]	0.19	0.059	3.3
(Carlson *et al*)[a]	Standard CI[b]	(0.12–0.30)	(0.030–0.12)	(1.9–5.8)
In vivo	Wang *et al*[a]	0.15	0.048	3.1
	Fowler *et al*[a]	0.04	0.027	1.5

[a] See text for detailed references.
[b] Means and standard confidence intervals (CI) are based on the log-normal distribution.

The start time for tumour repopulation

Drs Daşu and Fowler raised the issue about the starting time of repopulation of tumour cells that survive the treatment. Their concerns have been addressed in our previous letter-to-the-editor (Wang et al 2003c). Here, we would like to add a few more comments.

We agree with Drs Daşu and Fowler that the assumptions on the repopulation parameters play an important role in the analysis of *permanent brachytherapy* data; however, it should be insignificant for the data analysis of external-beam radiotherapy (EBRT) and high-dose-rate (HDR) radiotherapy. An analysis of clinical data from an HDR study by Brenner *et al* (2002) produced an α/β of 1.2 Gy, a value which is consistent with the 1–2 Gy range advocated by Drs Daşu and Fowler. However, the HDR data used by Brenner *et al* (2002) cannot be used to determine a unique set of values for α and α/β (Wang et al 2003b). These parameter identifiability issues can be overcome by combining the HDR data with additional data from an EBRT study conducted at MSKCC (Levegrün et al 2001). An analysis of the combined dataset gave a point estimate for α of 0.14 Gy^{-1} and a point estimate for α/β equal to 3.1 Gy (Wang *et al* 2003b). These estimates are consistent with the values reported earlier for a combined analysis of EBRT and permanent implant brachytherapy (Wang *et al* 2003a). The results of these analyses show that the 3.1 Gy estimate for α/β (Wang *et al* 2003a) is not sensitive to repopulation effects, as suggested by Drs Daşu and Fowler.

In vivo dose–response

Clinical data compiled from multi-institution, multi-modality studies tend to show a flat dose–response curve when compared to clinical data for a single-institution. Consequently, the analysis of multi-institution, multi-modality studies tends to result in low estimates for α (Fowler *et al* 2001 and Chappell *et al* 2004). Because of potential inconsistencies and uncertainties in clinical data from multi-institution, multi-modality studies, we feel that to verify the intrinsic dose–response, it is more appropriate to use single-institution and single-modality data.

Figure 1 shows a comparison of the tumour control probability (TCP) predicted using two sets of LQ radiosensitivity parameters—solid curves: $\alpha = 0.15$ Gy^{-1}, $\alpha/\beta = 3.1$ Gy (Wang *et al* 2003a, 2003b) and dashed curves: $\alpha = 0.04$ Gy^{-1}, $\alpha/\beta = 1.5$ Gy (Brenner and Hall 1999, Fowler *et al* 2001). The predicted TCP values are compared to the single-institution EBRT dose escalation study conducted at MSKCC (Levegrün *et al* 2001). The predicted TCP values obtained with the Wang *et al* parameters show good agreement with the clinical data. The goodness-of-fit (χ^2) was 3.1, which is much lower than the number of degrees of freedom for the χ^2 fitting ($\nu = 6$). In contrast, the shape of the TCP curve obtained $\alpha = 0.04$ Gy^{-1}, $\alpha/\beta =$ 1.5 Gy is much flatter than the one suggested by the clinical data. The goodness-of-fit obtained with the Fowler *et al* parameters is about 17, which is much larger than the number of degrees of freedom, ν.

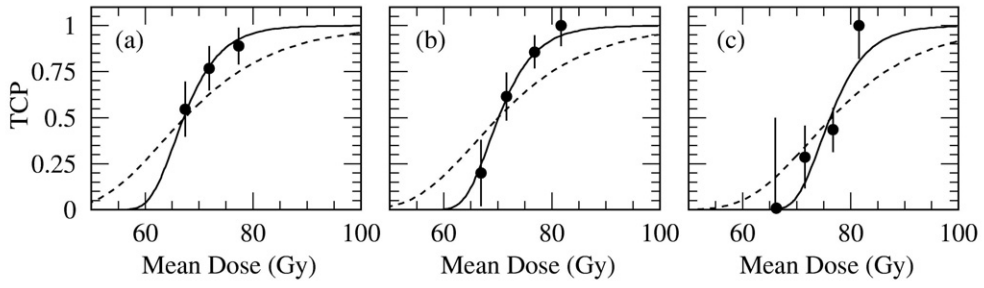

Figure 1. Dose–response of (a) low-risk, (b) intermediate-risk and (c) high-risk prostate cancer patients. Symbols represent clinical data of external-beam radiotherapy collected at Memorial Sloan-Kettering Cancer Center (Levegrün *et al* 2001). Curves represent model calculations based on two sets of LQ parameters—solid curves: $\alpha = 0.15$ Gy^{-1}, $\alpha/\beta = 3.1$ Gy (Wang et al 2003a, 2003b) and dashed curves: $\alpha = 0.04$ Gy^{-1}, $\alpha/\beta = 1.5$ Gy (Brenner and Hall 1999, Fowler *et al* 2001).

Conclusions

As we stated in Carlson *et al* (2004), the confidence intervals for α/β in all six of the published studies analysing clinical data overlap with each other. This statement is true even though the authors made different assumptions about the significance of repopulation effects for permanent brachytherapy treatment. However if the published estimates for both α and α/β are considered, the *in vitro* data reported in Carlson *et al* (2004) clearly favour the estimates reported by Wang *et al* (2003a), Wang *et al* (2003b) and Kal and Van Gellekom (2003) over those reported by others (Brenner and Hall 1999, Fowler *et al* 2001, Brenner *et al* 2002). However, given the uncertainties associated with the analyses of the clinical data and the uncertain relationship between *in vitro* and *in vivo* radiosensitivity parameters, we believe that additional data are needed to fully resolve the issue of whether α/β is closer to 1–2 Gy or 3–4 Gy. Regardless, we agree with Drs Daşu and Fowler that such low α/β values indicate a potential therapeutic gain for hypofractionation. We look forward to resolving this debate when additional clinical data become available, especially data from hypofractionation studies.

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