LETTER TO THE EDITOR

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

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Reply to ‘Comments on ‘Comparison of in vitro and in vivo $\alpha/\beta$ ratios for prostate cancer’’

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The Editor,

Sir,

We thank Drs Dašu 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 $\alpha/\beta$ 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 $\alpha/\beta$, and we agree with Drs Dašu and Fowler that our findings have potentially important implications for the treatment of prostate cancer using hypofractionation. However, Drs Dašu and Fowler argue in their letter that $\alpha/\beta$ 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 $\alpha/\beta$ derived from in vitro data. All of the point estimates for $\alpha$ are larger than 0.09 Gy$^{-1}$, and point estimates of $\alpha/\beta$ 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 $\alpha$, $\beta$ and $\alpha/\beta$. 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 $\alpha$ and $\alpha/\beta$ reported by Brenner and Hall (1999) are the same as those reported by Fowler et al. (2001). Estimates of $\alpha$, $\beta$ and $\alpha/\beta$ 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 $\alpha$, $\beta$ and $\alpha/\beta$ reported by Fowler et al. (2001) are outside of the standard CI. Estimates for $\alpha$ 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 $\alpha$ versus $\beta$ 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 $\alpha$ and $\beta$ 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.

<table>
<thead>
<tr>
<th>LQ Parameters</th>
<th>α (Gy⁻¹)</th>
<th>β (Gy⁻²)</th>
<th>α/β (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>Meanb</td>
<td>0.19</td>
<td>0.059</td>
</tr>
<tr>
<td>(Carlson et al)</td>
<td>Standard CIb</td>
<td>(0.12–0.30)</td>
<td>(0.030–0.12)</td>
</tr>
<tr>
<td>In vivo</td>
<td>Wang et ala</td>
<td>0.15</td>
<td>0.048</td>
</tr>
<tr>
<td>Fowler et alb</td>
<td>0.04</td>
<td>0.027</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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 Da¸su 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 Da¸su 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 Da¸su 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 Da¸su 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: α = 0.15 Gy⁻¹, α/β = 3.1 Gy (Wang et al 2003a, 2003b) and dashed curves: α = 0.04 Gy⁻¹, α/β = 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 (χ²) was 3.1, which is much lower than the number of degrees of freedom for the χ² fitting (ν = 6). In contrast, the shape of the TCP curve obtained α = 0.04 Gy⁻¹, α/β = 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.
Conclusions

As we stated in Carlson et al (2004), the confidence intervals for $\alpha/\beta$ 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 $\alpha$ and $\alpha/\beta$ 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 $\alpha/\beta$ is closer to 1–2 Gy or 3–4 Gy. Regardless, we agree with Drs Daşu and Fowler that such low $\alpha/\beta$ 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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