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Original Article

Is Biochemical Relapse-free Survival After Profoundly Hypofractionated Radiotherapy Consistent with Current Radiobiological Models?

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Abstract

Aims: The α/β ratio for prostate cancer is thought to be low and less than for the rectum, which is usually the dose-limiting organ. Hypofractionated radiotherapy should therefore improve the therapeutic ratio, increasing cure rates with less toxicity. A number of models for predicting biochemical relapse-free survival have been developed from large series of patients treated with conventional and moderately hypofractionated radiotherapy. The purpose of this study was to test these models when significant numbers of patients treated with profoundly hypofractionated radiotherapy were included.
Materials and methods: A systematic review of the literature with regard to hypofractionated radiotherapy for prostate cancer was conducted, focussing on data recently presented on prostate stereotactic body radiotherapy. For the work described here, we have taken published biochemical control rates for a range of moderately and profoundly fractionated schedules and plotted these together with a range of radiobiological models, which are described.
Results: The data reviewed show consistency between the various radiobiological model predictions and the currently observed data.
Conclusion: Current radiobiological models provide accurate predictions of biochemical relapse-free survival, even when profoundly hypofractionated patients are included in the analysis.

Key words: Hypofractionation; prostate; radiobiology; stereotactic

Introduction

The α/β ratio is a way of expressing the sensitivity of tumours and surrounding normal tissue to changes in fraction size. For most cancers the α/β ratio is high (around 10 Gy), indicating that these tissues are more sensitive to total radiation dose than dose per fraction. For the late-reacting surrounding normal tissues, the α/β ratio is low (around 3), indicating a higher sensitivity to fraction size.

It is hypothesised that the effective α/β ratio for prostate cancer cells is lower than that of surrounding normal tissue, and may be as low as 1.5 Gy [1–8]. This would suggest that hypofractionated regimens should result in the same tumour control probability as a conventional regime of 37–39 daily fractions. Not only would a shorter regimen be preferred by patients, but this will probably have important implications for cost-effectiveness. This paper is not proposing a new radiobiological model of prostate cancer, but we have used existing, well-established models to examine whether they continue to be consistent with emerging clinical evidence on profound hypofractionation or whether new data suggest that we should re-examine the radiobiological hypotheses on which these doses were determined.

Although the linear quadratic model remains the most commonly used in practice, it is thought to overestimate cell kill at a high dose per fraction [9]. Newer models, including the universal survival curve, may be more accurate at predicting lethal damage with large fraction sizes [10].

A systematic review has identified 18 series of moderate hypofractionation involving 3504 patients at doses per

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fraction between 2.5 and 4.0 Gy and 11 profoundly hypofractionated series using 7.7–10 Gy fractions, involving 1482 patients. Five year biochemical tumour control rates and late gastrointestinal and genitourinary grade 2 reactions have been tabulated. We review these series and then compare the biochemical outcomes with predictions from a variety of well-established radiobiological models.

Materials and Methods

Systematic Review Search Strategy

We conducted a systematic review using the search terms 'prostate AND hypofractionated' or 'hypofractionation AND prostate AND radiotherapy' or 'fractionation AND prostate AND cancer'. Studies, written in English, were included if they contained more than 30 patients treated with hypofractionated external beam photon therapy without high dose rate or nodal irradiation.

Initial searches produced 137 records. Fifty-one were selected for further review of the abstract and of these the full text paper was assessed in 37 cases. Selected papers reported prospective or retrospective cohorts or trials of at least 30 patients treated with a hypofractionated photon radiotherapy regimen (defined as more than 2 Gy/fraction) and reported biochemical outcomes and/or standardised toxicity data. Studies were excluded if they used a mixture of modalities (e.g. brachytherapy and external beam) or if the whole pelvis was treated.

A second pubmed search was carried out using the search terms 'prostate stereotactic radiotherapy'. This resulted in 130 records. Papers were selected if they described clinical cohorts of prostate cancer patients treated with >5 Gy/fraction as monotherapy. This resulted in 15 papers, which were selected for full text review. In addition, selected work presented at international conferences and published in abstract form was also included.

Conversion Between Fractionation Schemes

Cell survival curves from laboratory experiments show a decrease in the proportion of viable cells with increasing dose. This relationship is, however, not linear: the natural of the logarithm of the survival fraction is described by a quadratic equation with linear term α proportional to dose and β proportional to the square of dose.

The α component can be interpreted as the likelihood of 'single-hit' damage, which produces the linear part of the cell survival curve. The β component can be interpreted as describing 'double-hit' damage, the probability of which shows dose-rate dependence. The ratio α/β is therefore a measure of relative fraction size sensitivity of a particular tissue or cell type.

In order to compare dose prescriptions delivered with differing fractionation schemes, we converted all schedules to the biologically equivalent dose in 2 Gy fractions, EQD_2, using the following equation:

$$EQD_2 = \frac{N_1 d_1 \left(\frac{\alpha}{\beta} + d_1\right)}{\left(\frac{\alpha}{\beta} + 2.0\right)} \quad [1]$$

where N_1 is the number of fractions of size d_1. Repopulation effects are neglected, as it has been shown that accelerated repopulation effects do not improve model fits to most existing clinical data [6,7]. For this work and in all the models described below we have assumed an α/β ratio of 1.4 Gy for all risk groups, in keeping with recent published work [7] (α/β ratio = 1.4 Gy, 95% confidence interval 0.9–2.2 Gy).

Models of tumour control probability (TCP) for the prostate

A number of models have been proposed in the literature to describe the radiation dose–response of prostate cancer. A mechanistic approach was adopted by Brenner and Hall [1], who used the linear quadratic model to describe the probability of avoiding biochemical failure (bNED) at 5 years for dose D, thus:

$$bNED_{LQ}(D) = \exp\left[-K\exp\left(-\alpha D - G\beta D^2\right)\right] \quad [2]$$

where K is related to the initial number of potential stem cells, which was assumed to be linearly proportional to the mean prostate-specific antigen (PSA) over each cohort, G accounts for fractionation, taking a value of 1/24, and an α/β ratio of 1.5 Gy (95% confidence interval 0.8–2.2). This parameterisation was modified using additional clinical data [3] to α/β = 1.2 Gy (95% confidence interval 0.03–4.1) with the value of K of 138. A similar form of the linear quadratic model was recently presented by Miralbell *et al.* [7], where the biochemical relapse-free survival at 5 years was expressed as:

$$bRFS_{Miralbell}(D) = \exp\left[-\exp\left(k - \alpha D - \alpha\left(\frac{\beta}{\alpha}\right)\frac{D^2}{N}\right)\right] \quad [3]$$

where D is the total dose delivered in N fractions and k can be interpreted as the natural log of the effective target cell density. The form of the model presented here neglects accelerated repopulation. For this work we will take the parameter values fitted by Miralbell *et al.* to data for groups of low-, intermediate- and high-risk patients without androgen deprivation (low risk: α = 0.019, k = 2.8; intermediate risk: α = 4.5, k = 0.032; high risk: α = 0.041, k = 5.3). A value of α/β = 1.4 was used for all risk groups.

In contrast to the linear quadratic-based models, Fowler [8] took a purely empirical approach and fitted a logistic model to data from 17 clinical studies of external beam radiotherapy and brachytherapy published between 1995 and 2000.

Their fitted curve used a slope parameter b of 0.124 (95% confidence interval 0.094–0.155) and 0 Gy intercept a of −8.14 (95% confidence interval −10.33 to −5.95) to describe intermediate-risk patients (PSA 10–20 ng/ml or biopsy Gleason score ≥7 or stage T2b–T2c). More recently, King and Kapp [11] also applied a logistic model functionally