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Confirmation of a low α/β ratio for prostate cancer treated by external beam radiation therapy monotherapy using a post-treatment repeated measures model for PSA dynamics

Cécile Proust-Lima PhD[1,2], Jeremy MG Taylor PhD[3,4], Solène Sécher PhD[1,2], Howard Sandler MD[5], Larry Kestin MD[6], Tom Pickles MD[7], Kyoungwha Bae PhD[8], Roger Allison FRANZCR[9], Scott Williams MD FRANZCR[10]

[1] INSERM, U897, Epidemiology and Biostatistics Research Center, 33076 Bordeaux, France

[2] University Victor Segalen, 33076 Bordeaux, France

[3] Department of Biostatistics, University of Michigan, Ann Arbor, MI

[4] Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

[5] Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA

[6]Department of Radiation Oncology, Beaumont Hospital, Royal Oak, MI

[7]British Columbia Cancer Agency, Vancouver, British Columbia, Canada

[8]Radiation Therapy Oncology Group, Philadelphia, PA

[9]Division of Oncology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

[10]Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Corresponding author:

Dr Scott Williams

Division of Radiation Oncology

Peter MacCallum Cancer Centre

Locked Bag 1 A'Beckett St

Victoria 8006 Australia

email: scott.williams@petermac.org

phone: +61 3 9656 1111

fax: +61 3 9656 1424

Running title: Estimation of α/β ratio of prostate cancer using repeated post-treatment PSA measures

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ABSTRACT

Purpose: To estimate the α/β ratio of prostate cancer treated with external beam radiation only using a model of long term prostate specific antigen (PSA) dynamics.

Materials and methods: Repeated measures of PSA from 5,093 patients from 6 institutions treated for localized prostate cancer by external beam radiation therapy (EBRT) without planned androgen deprivation were analysed. A biphasic linear mixed model described the post-treatment evolution of PSA, rather than a conventional model of time to biochemical recurrence. The model was adjusted for standard prognostic factors (T-stage, initial PSA and Gleason) and cohort specific effects. The radiation dose fractionation effect was estimated from the long term rate of rise of PSA.

Results: Adjusted for other factors, total dose of EBRT and sum of squared doses per fraction were associated with long term rate of change of PSA (respectively p=0.0017 and p=0.0003), an increase of each being associated with a lower rate of rise. The ratio α/β was estimated at 1.55Gy (95% confidence bands 0.46, 4.52Gy). This estimate was robust to adjustment of the linear mixed model.

Conclusions: Analysing a large EBRT-only cohort along with a method that utilises all the repeated measures of PSA after end of treatment, a low and precise α/β was estimated. These data support the use of hypofractionation at fractional doses of 1.8-2.8Gy, but cannot presently be assumed to accurately represent higher doses per fraction.

Keywords: Prostate cancer, Prostate-specific Antigen, Progression of disease, Radiation therapy, Alpha/beta, Radiosensitivity

The radiation oncology literature is permeated with suggestions that the apparent sensitivity of prostate cancer to hypofractionated radiotherapy is a valuable therapeutic target (1-4). When quantifying the dose and dose-per-fraction (DPF) relationship with a linear-quadratic biological model, the consensus is that the derived α/β ratio is substantially lower in prostate cancer than in most cancers, with typical purported values between 1 and 3Gy (3, 5-7). While we are yet to see any prospective controlled studies to confirm these observational data, the hypothesis generated by them is that larger DPF therapies may be optimal therapy in this cancer, which has been incorporated into several clinical techniques (8-10).

In applying the available radiobiology knowledge to clinical protocols in prostate cancer, α/β ratio estimates which have displayed the tightest estimates are, quite understandably, those which clinicians have relied on. These estimates have unfailingly used external beam radiation therapy (EBRT) in combination with brachytherapy data to date. From a modelling viewpoint, this combined data is required as it enables one to either: theoretically eliminate the β component from calculations involving the low-dose-rate (LDR) brachytherapy data (3, 6, 11); or to have access to large enough DPF variation to successfully model both the α and β components by using hypofractionated high-dose-rate (HDR) brachytherapy data (5, 7). Each of these approaches can be criticized on a number of fronts, such as including yet not accounting for uncertainties associated with comparing the relatively homogenous dose of EBRT to highly inhomogenous brachytherapy dose distributions (12). Inherently, these combined modality data should not be extrapolated to the design of EBRT-only fractionation strategies.

A more acceptable approach would be to derive the α/β ratio from fractionation studies incorporating EBRT only. Unfortunately, the largest randomised study to date comparing conventional DPF and hypofractionation (13) has failed to provide precise estimates (14), while data from observational models is similarly imprecise when using only EBRT data (7). One constant throughout all the previous studies has been the use of a conventional binary failure endpoint to assess outcome, such as a time-to-recurrence endpoint (biochemical or clinical). Yet, repeated measures of PSA are collected after therapy; the evolution of which can be described using a linear mixed model. We have previously provided a framework for evaluating prognostic and other factors that may be associated

with disease progression in such a model of prostate cancer (15). By incorporating the complete PSA history, rather than reducing it to a somewhat arbitrary single point, such as biochemical recurrence, this modelling approach has the potential to greatly increase the power with which prognostic variables can be interpreted. A finding from previous work (15) using this mixed modelling strategy was that the dose of radiation was associated with the pattern of post treatment PSA values, but that given the pattern of PSA the dose of radiation provided no further significant information about clinical recurrence. This provides a rationale for the approach in the current paper where we are investigating the effect of the radiation fractionation schedule on disease progression and we can do that by using just the linear mixed model approach focussing on the PSA values after treatment and not considering clinical recurrence. The present studies aim is to use this modelling strategy to attempt to describe the α/β ratio using data from a large number of men treated with EBRT containing little dose inhomogeneity, where this has been unable to be done prior with adequate precision.

METHODS AND MATERIALS

Patient cohorts

The analysis included all patients treated for a prostate cancer by external beam radiation therapy (EBRT) from 6 different cohorts: University of Michigan, Ann Arbor, Michigan (UM) (16), Radiation Therapy Oncology Group (RTOG 9406) (17), Peter MacCallum Cancer Center, Melbourne, Australia (PMCC) (18), William Beaumont Hospital, Detroit, Michigan (WBH) (19), Royal Brisbane Hospital, Brisbane, Australia (RBH) (20) and British Columbia Cancer Agency, Vancouver, Canada (Vancouver) (21). Loco-regional and systemic disease was assessed at the discretion of the treating physician, and typically included computed tomography of the abdomen and pelvis, along with whole body bone scanning. Surgical staging of lymph nodes was done in <1% of cases. Those having planned neoadjuvant or adjuvant androgen deprivation therapy (ADT) were ineligible. All patients had clinically localized prostate cancer of clinical stage T1 to T4 and were node and metastasis negative. All data were acquired under Institutional Review Board approval at the respective institutions and at UM, where the data were aggregated and analysed.

In summary, EBRT (either 2D or 3D conformal) was targeted to the prostate or prostate plus seminal vesicles depending on clinical risk. Whole pelvic radiotherapy was not routinely performed. All cases were required to have at least one year follow-up without clinical recurrence or salvage ADT and at least two PSA measurements before end of follow-up. All PSA measures collected after EBRT until the end of follow-up (minimum time to clinical recurrence or lost to follow-up) or initiation of salvage ADT were analysed. PSA measures were logarithmically transformed using ln(PSA+0.1 ng/mL) to satisfy the normality assumptions for inclusion in the statistical models.

Three prognostic factors were used in the analysis: the initial level of PSA at diagnosis (iPSA; transformed on the continuous scale to iPSA=ln(iPSA+0.1)), T-stage category (1, 2, 3-4) and Gleason score (GS; ≤6, 7, 8-10). Dose of radiation D was defined as the sum of all fractional doses d_j given during the J sessions of therapy $\left(D = \sum_{j=1}^{J} d_j\right)$. To evaluate the α/β ratio, squared dose D^2 was defined as the sum of all squared fractional doses given during the therapy $\left(D^2 = \sum_{j=1}^{J} d_j{}^2\right)$. The α/β is the ratio of the regression parameters of D and D^2 in accordance with the linear-quadratic biological model. The mean dose per fraction was defined as the average dose per fraction received over sessions $\left(\bar{d} = \sum_{j=1}^{J} d_j \Big/ J\right)$.

Statistical analysis

Distributions of prognostic factors over cohorts were compared using Kruskall-Wallis test for continuous variables and Chi-square test for categorical variables. Change over time of PSA after end of radiation therapy was described using a linear mixed model (LMM) (22). Evolution of PSA was separated into 3 components as proposed by Proust-Lima et al. (15) and described in figure 1: (1) post-treatment level of PSA, denoted as post-treatment PSA (ptPSA) ; (2) short term evolution during the first year after end of EBRT, approximated by $f_1(t)=((1+t)^{-1.5}-1)$ and denoted as short term drop of PSA (stPSA) ; (3) long term evolution of PSA, described by a linear trend and denoted as long term rise of PSA (ltPSA).

The linear mixed model accounted for inter-individual variability through individual correlated Gaussian random-effects for each component (ptPSA, stPSA and ltPSA), as well as intra-individual correlation

through correlated errors in addition to the independent Gaussian measurement errors (detailed in Appendix eI). The full model was adjusted for iPSA, T-stage and GS, and their interactions with short term drop and long term rise of PSA. The α/β ratio was derived from the dose and squared dose effect evaluated on long term PSA rise. The analysis also adjusted for the dose and squared dose effects on post-treatment level of PSA and short term drop of PSA. A sensitivity analysis examined a proposed parsimonious model (15). Associations were tested using the Wald test and likelihood ratio test (LRT). For the pooled data, cohort-specific intercepts, short term drops and long term rises were included to correct for cohort heterogeneity. The α/β ratio was estimated as the ratio of the effect of dose and squared dose on long-term rise of PSA. Confidence bands (CB) were obtained from the profile likelihood as described in the appendix. Statistical analyses were performed with SAS statistical software version 9.1.3 (SAS Institute, Cary, NC). Statistical tests were at the two-sided α=0.05 level of significance.

RESULTS

Description of cohorts

Summary variables for he 6 cohorts are described in Table 1. The median follow-up was 4.7 years, with relatively shorter time of follow-up for UM and WBH (respectively a median of 4.1 and 3.7 years) and longer time for RBH with a median of 5.3 years. The prognostic factor distribution differed significantly over cohorts ($p<0.0001$ for each factor). RTOG included more T-stage 1 and less T-stage 3 and 4 while PMCC and Vancouver had a converse distribution. The proportion of patients having a GS of 7 varying from 19.9% for BM to 37.4% for UM, while high grade cancers were relatively less frequent in the PMCC data (4.8%) than at WBH (9.0%). Finally, the median institutional pre-treatment PSA level ranged from 7.4 ng/mL for RTOG to 15.0 ng/mL for RBH.

Total dose of EBRT and dose per fraction

A large range of total dose of EBRT was observed (50 - 84.6Gy). The total dose distribution varied significantly across cohorts ($p<0.0001$) from a median of 63.2Gy to 78.0Gy for RBH and RTOG respectively (Table 1). The dose per fraction varied from 1.70Gy to 2.77Gy varied significantly across cohorts ($p<0.0001$) from a median of 1.80Gy for WBH to 2.11Gy for RBH.

α/β estimation

Parameter regression coefficients for dose and squared dose using the biphasic linear mixed model are given in Table 2. Total dose of EBRT was associated with post-treatment initial level of PSA (p=0.0002); a higher total dose being associated with a lower post-treatment level of PSA. Fractional dose was not associated with post-treatment PSA level (p=0.876). Neither dose nor squared dose were significantly associated with the short term drop of PSA (respectively p=0.135 and p=0.163). The total dose and squared dose were highly associated with long term PSA rise, with both higher total doses (p=0.0017) and doses per fraction (p=0.0003 associated with a lower long term rate of rise of PSA. This association led to an estimation of α/β =-0.0062/-0.0040=1.55Gy with 95%CB of 0.46Gy to 4.52Gy.

Robustness of the estimate

To evaluate whether this estimate was robust to specification of the linear mixed model, we compared the estimate of α/β for different specifications of the structure of correlation of the repeated measures, different adjustment for prognostic factors and different adjustment for dose on post-treatment PSA and short term drop of PSA. Using complete or parsimonious adjustment for prognostic factors did not substantially change the estimate of α/β nor its 95% confidence band (α/β=1.58, 95%CB=0.46; 4.69). Accounting for the correlation between repeated measures of PSA improved markedly the fit of the data (log-likelihood improved by 3200 points). The estimate of α/β was slightly reduced if independent errors were assumed (α/β=1.15, 95%CB =0.24; 3.23). Not adjusting for squared dose on post-treatment PSA or short term drop of PSA gave α/β=2.37 (95%CB =0.83; 7.63), while when adjusting only for dose on the post-treatment level of PSA, α/β=1.64 (95%CB =0.38; 5.96). This hence highlights the need for the appropriateness of complete adjustment as used in the principal analysis.

Variability over cohorts

The variability between cohorts due to their heterogeneity in recruitment, time period and other unknown factors was accounted for by including cohort-specific mean trajectory parameters. This greatly improved the goodness-of-fit of the model (the log-likelihood was improved by 108 points). There were significant differences between cohorts in the initial post-treatment level, probably reflecting differences between the patient populations that were not accounted for by the other

prognostic factors. There were also small differences in the rate of rise of PSA. However, not including this adjustment for cohort effects did impact the α/β estimate (α/β=10.6) with only the RBH cohort data changing the α/β ratio estimate range. Excluding this dataset led to a still low α/β (3.16Gy) with larger CB (95%CB=0.95; 21.20Gy) while excluding one of the 5 other cohorts led to α/β ratios from 1.14 to 1.53Gy. These findings are plausible given that the RBH data has the largest dose per fraction variation and hence the largest impact on the α/β ratio.

As a sensitivity analysis we adjusted for interactions between prognostic factors and cohorts, and adjusted for the year of treatment that could have explained differences over cohorts. The estimate of α/β remained in the same range as for the main analysis (α/β=1.47 and α/β=2.02 respectively). Using the complete model, we estimated the α/β ratio separately for each cohort (Table 3). Estimates of α/β varied greatly from cohort to cohort. However, except for RTOG and Vancouver, wide confidence bands allowed for extremely low value of α/β as well as infinitely large values and suggests that the α/β ration cannot be derived from individual cohorts.

α/β estimation for subgroups of prognostic factors

We evaluated whether the α/β was different when considering subpopulation of patients with different prognostic factors values: T1, T2 and T3-4; Gleason≤6, 7 and 8-10; iPSA≤10ng/mL or >10ng/mL. The fully-adjusted linear mixed model was then derived within each of these subgroups and the resultant dose and squared dose parameters are given in Table 4. For some of the subgroups the effect of dose and dose squared are not statistically significant. This occurred in the smaller subgroups that tended to have more advanced disease. Except for the Gleason 8-10 category, estimates of α/β remained very low varying from α/β=-0.90 to α/β=2.88. Among subjects with GS 8-10, α/β was estimated close to 20 but with a lack of precision (95% confidence bands -∞; +∞).

DISCUSSION

The design of optimal radiation fractionation schedules to treat prostate cancer is an active area of clinical research presently. The consensus for a low α/β ratio in prostate cancer via a number of modelling studies (3, 5-7) has produced a groundswell of support for schedules incorporating large doses per fraction, with considerable early implementation using high dose-rate brachytherapy in

particular (10). EBRT techniques have also been designed to meet these theoretical benefits (23), despite requiring an assumption that combined EBRT and brachytherapy data can be directly extrapolated to the EBRT monotherapy situation. The present data support the low α/β ratio consensus, but are set apart by a lack of reliance on the inclusion of brachytherapy results to derive accurate estimates.

Drawing from summary outcome data, early clinical α/β ratio models based on EBRT and low dose-rate brachytherapy (LDRB) data (3, 6) produced α/β ratio estimates which appeared consistent at 1.5Gy with great precision. These analyses were to some extent reliant on assumptions that both the dose-rate and the dose homogeneity differences between treatment modalities did not require accounting for. Subsequent avoidance of the dose-rate assumption by deriving estimates from combined EBRT and high dose-rate brachytherapy (HDRB) results also arrived at a very similar (1.2Gy) estimate (5). Further to these studies, we focussed on replacing the previously used grouped outcome data with that of the individual patient to enable better potential control of confounding factors, using multivariable techniques (7). With EBRT data alone (to avoid dose inhomogeneity), a model based on a standard binary actuarial bF endpoint was unable to estimate the α/β ratio (95%CI 1.1Gy to infinity) despite having >3000 men and >100 unique fractionation schedules to analyse. Incorporation of the very large fractional doses from a relatively small number of HDRB boost cases was necessary to substantially improve the estimate precision to 2.6Gy (95%CI 0.9-4.8Gy). These estimates were dependent on the specification of the HDRB dose however, suggesting that dose homogeneity, and the manor in which it was accounted for, can be a potential influencing factor within a modelling system incorporating homogenous (EBRT) plus inhomogenous (brachytherapy) dose data. Our present data suggesting a low α/β ratio in patients all treated with a homogenous dose and constant fraction size are therefore both unique and reassuring in light of the previous assumptions.

The present data support a most likely α/β ratio of 1.5Gy, but suggest confidence limits which have a range of 0.5-4.5Gy. This range is similar to previous studies using HDRB data (5, 7), but wide in comparison to the range of values suggested in both the LDRB-based analyses (with values of 95%CI 0.8-2.2Gy (3) and 1.3-1.8Gy (6)). In employing these data to the design of clinical fractionation schedules, consideration need be given to such estimate uncertainties. Taking the present data as

being the most directly applicable to the situation of EBRT monotherapy, the design of hypofractionation schedules should go beyond deriving a dose and fractionation at only an α/β ratio of 1.5Gy. Importantly, consideration should also be given to what detriment there may be to a new schedule should the value be at either end of the plausible α/β ratio range. For instance, a protocol of 36Gy in uniform 6 fractions may be suggested as approximately isoeffective with 78Gy in conventional 2Gy fractions at an α/β ratio of 1.5Gy. However, at an α/β ratio of 4Gy this isoeffect would fall to that of just 60Gy (as an equivalent in 2Gy fractions), with an attendant reduced efficacy likely. Even if the α/β ratio is 1.5Gy, some men will undoubtedly have a low α/β ratio and some a higher one, which will create a spread of outcomes which will be more apparent as the DPF increases – those with low or average values will do as well or better than conventional fractionation, but those with a higher α/β ratio will have an over-representation of poor biologically effective doses in the hypofractionated group. In practical terms, a move to hypofractionation with EBRT with uniform large fraction sizes throughout the course would most safely be done by judiciously maintaining the overall total dose, so that if the α/β ratio is ultimately suggested to not be as low as expected, the hypofractionated patients still receive a biologically useful radiation dose.

An apparent biological phenomenon suggested by the model revolves around the differing impact of radiation dose and DPF at various phases of PSA evolution. Although both phases of PSA evolution are related to iPSA, GS and T-stage, the rate of PSA fall early after EBRT appears dependent on a biological system unaffected by the amount of radiation injury. Conversely, a rising PSA profile indicative of recurrence shows a strong and independent correlation to EBRT dose and DPF. In relation to existing studies, most have looked at the nadir PSA level or the time taken to reach that point rather than the pure “halving” time. A low PSA nadir at a late time has been the most consistent favourable feature identified in a number of these studies (24, 25), and would be plausible based on these data which suggest an advantage for indolent cancers which have undergone a large therapeutic outcome. Further biological insights from subset analyses of know prognostic factors were not forthcoming. For the subdivisions of T-stage, iPSA and GS analysed, there was no consistent trend to the estimated α/β ratio. Small numbers of cases in the T3 or GS 8-10 categories precluded confident estimates to be made. As with our previous analysis (7), plausible biological suggestions

that high grade cancers may have a higher α/β ratio, secondary to a higher growth rate, continue to be unsupported.

For the first time, the α/β ratio of prostate cancer has been directly estimated from the effect of dose on the longitudinal change of PSA. This has certain advantages over the use of a conventional biochemical failure endpoint in this situation. By using the evolutionary pattern of all the repeated measures of PSA as an outcome, the power of the analysis is greatly increased; enabling confidently modelling of the small changes in fractionation seen in EBRT data. Sensitivity analysis has shown the α/β ratio estimates to be robust to model misspecification (α/β ratio between 1.2 and 2.4Gy depending on model), although the model incorporating all the PSA evolution phases proved to have the optimal performance. From our previous experience in both development (16) and validation (15) of this modelling system, the complexities of the model do appear justified, with a demonstrated ability to accurately predict both PSA evolution and associated clinical failure risk. However, we found that whether or not we adjusted for cohort differences changed considerably the estimate. Each cohort had a different distribution of prognostic factors and different range of fractionation schedules, especially the RBH data. The RBH data had higher doses per fraction than the other cohorts, and these data were most influential in determining the α/β ratio.

While we did perform a considerable amount of sensitivity analysis and adjusted for known prognostic factors there remains the potential that the results are biased by other confounding factors. Thus the results should be interpreted with some caution. Patients were recruited at different times over a 17 year window, changes in treatment planning and administration have occurred, and the criteria for assigning a GS may have also drifted. As observational data, the dose given to each patient was chosen partially based on that patients prognostic factors, while we adjusted for known prognostic factors other prognostic factors may have been important for some patients. As a result, adjustment for cohort variability was the only way to provide an estimate of the ratio α/β that was adjusted as best as possible for this heterogeneity over cohorts. As with all other analyses of this topic, adjustment for cohort or other measured factors cannot prevent bias in the estimate of α/β from other unknown influential factors.

In conclusion, we propose that EBRT fractionation schemae can be modelled using a low α/β ratio, for a dose per fraction range of 1.7-2.8Gy without androgen deprivation therapy. Hypofractionation beyond this level should still be regarded as unsupported by clinical evidence, as no homogenous dose data presently exist to confirm that the model holds true at more ablative fractionation schedules. Prospective studies continue to be highly anticipated in this regard.

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Figure legends

Figure 1: Evolution of PSA after end of radiation therapy: post-treatment level of PSA, short term drop of PSA and long term rise of PSA.