What do we know about the α/β for prostate cancer?

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Since last decade, the debate on the parameter which reflects prostate cancer sensitivity to fractionation in a radiotherapy treatment, the α/β, has become extensive. Unlike most tumors, the low labeling indices (LI) and large potential doubling time that characterize the prostate tumor led some authors to consider that it may behave as a late responding tissue. So far, the existing studies with regard to this subject point to a low value of α/β, around 2.7 Gy, which may be considered as a therapeutic gain in relation to surrounding normal tissues by using fewer and larger fractions. The aim of this paper is to review several estimates that have been made in the last few years regarding the prostate cancer α/β both from clinical and experimental data, as well as the set of factors that have potentially influenced these evaluations. © *2012 American Association of Physicists in Medicine*. [http://dx.doi.org/10.1118/1.4712224]

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I. INTRODUCTION

In radiotherapy (RT), the sensitivity to changes in fractionation can be quantified in terms of the α/β ratio.[1] It is widely accepted that α/β values for most human tumors are high (typically 10 Gy), showing lower fractionation sensitivity than late responding normal tissues (typically 3 Gy).[2] However, there are some exceptions, such as the melanoma[3] with α/β of 0.6 Gy and some sarcomas[4] with α/β of 0.4 Gy. Both tumors show low labeling indices (LI) and/or are slow growing, with a large potential doubling time (T_{pot}).[5]

Prostate tumors show both low LI values (<3%) and a very large T_{pot} with a median of 42 days,[6,7] resulting in a low proportion of cycling cells. Thus, prostate tumors are expected to respond to changes in fractionation as a late responding tissue.[8] Several recent studies have reported low α/β values for prostate cancer.[9–28] If this α/β is proven to be lower than values estimated for late complications, then hypofractionated regimens are expected to improve the therapeutic ratio,[8,29–36] beyond the advantages on cost saving and patient convenience.

Nevertheless, the question of how low the α/β ratio for prostate cancer is remains unanswered,[37–39] and many factors have been reported to contribute to the uncertainty about estimations of its value, such as heterogeneity of tumors[10,40] and interpatient variations,[41,42] influence of hypoxia,[42] onset of clonogenic cells repopulation,[15,17,26,41,43,44] repair during low-dose-rate brachytherapy (LDRBT),[11,15,17,26,41,44] value of the relative biological effectiveness (RBE) of permanent implants,[14,41,44,45] variations with clinical stage,[24–27,42] edema resulting from the insertion of radioactive seeds into the prostate,[17] dose heterogeneity of brachytherapy (BT) implants,[23,41] biological effectiveness of external-beam radiotherapy (EBRT) and LDRBT,[46] relevance of parameters determined *in vitro* and its relation to the *in vivo* environment,[18,42,47] use of combined data from multiple institutions with different modalities,[13] and imprecision of data assessed with only one modality.[20,23,27] Therefore, despite large evidence exists in favor of a low α/β ratio, caution must be taken when designing hypofractionated schedules, as small differences in its value may lead to marked changes in the calculated biologically effective dose (BED) delivered.

We will critically review the α/β ratio estimations for prostate tumor by applying radiobiology knowledge to clinical outcome as well as experimental *in vitro* data exploiting factors which have been reported to influence evaluations. Derivations from randomized clinical trials of hypofractionation and a trial from hyperfractionation will be also reviewed.

II. CLINICAL EVIDENCE OF A SMALL α/β

Brenner and Hall[9] were the first to point out the clinical evidence that prostate cancer should have a low α/β ratio. Two datasets on biochemical control—one from EBRT and other from LDRBT with ^{125}I implants—and the linear-quadratic (LQ) model were used for the analysis. These combined data were required to theoretically eliminate the β

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component from the LDRBT calculations (considering a complete repair of sublethal damage after LDRBT treatment) to estimate the α parameter. The β parameter was then generated with the EBRT data, considering the equivalence on biochemical control achieved using EBRT doses of 70 Gy in 1.8–2.0 Gy per fraction and 145 Gy from ^{125}I implants. An α/β of 1.5 Gy (95% CI 0.8, 2.2) was derived from this analysis. Proposals for the α/β ratio of prostate cancer of several investigators are summarized in Table I.

Fowler *et al.*[11] updated the comparison and analysis of Brenner and Hall[9] with a review of 17 clinical outcome papers in patients with prostate cancer treated either with EBRT or ^{125}I or ^{103}Pd implants. A direct analysis of the clinical data was performed to derive both the α/β ratio and the half-time of repair ($T_{1/2}$) of the prostate cancer. An α/β of 1.49 Gy (95% CI 1.25, 1.76) was obtained. Chappell *et al.*[19] added Lukka *et al.*[48] results on the clinical outcome of patients treated with hypofractionated EBRT to the previous analysis.[11] An α/β ratio of 1.44 Gy (95% CI 1.22, 1.76) was estimated, consistently with the first result.

Considering the equivalence on clinical outcomes of EBRT and LDRBT in the treatment of localized prostate cancer, King and Fowler[12] presented a simple analytical derivation of α/β without fitting models to clinical data. By applying the LQ formalism for fractionated EBRT and permanent LDRBT, an α/β of around 1.8 Gy considering ^{125}I implants and around 2 Gy with ^{103}Pd were derived.

III. THE TUMOR HETEROGENEITY EFFECT

King and Mayo[40] made some remarks to the work of Brenner and Hall[9] due to its extremely low radiosensitivity ($\alpha = 0.036$ Gy $^{-1}$) leading to an unrealistic too low number of clonogens (15.3 with the LDRBT dataset and from 53.4 to 302.3 using the EBRT data). The authors argued that those values had no biological relevance and were inconsistent between LDRBT and EBRT. They proposed that a solid tumor would consist of a heterogeneous population of clonogens with a spectrum of radiosensitivities. An α/β value of 4.96 Gy (95% CI 4.1, 5.6) was derived. Brenner and Hall[10] responded with a fully heterogeneous LQ model in which both α and β were represented by independent Gaussian distributions, resulting in an α/β of 2.1 Gy.

IV. THE INFLUENCE OF RBE, DOSE HETEROGENEITY OF BT, REPOPULATION, AND $T_{1/2}$

Dale and Jones[45] criticized Brenner and Hall[9] and Fowler *et al.*[11] estimations for not taking into account the RBE of the radiation emitted by permanent implants of ^{125}I and ^{103}Pd. The RBE contribution results in the enhancement of BED (Refs. 49 and 50) and is likely to be between 1.2 and 2.1 for ^{125}I sources[51–55] and between 1.6 and 2.3 for permanent ^{103}Pd implants.[53–55] Chappell *et al.*[14] recalculated the α/β estimates of Fowler *et al.*[11] by combining RBEs for ^{125}I and ^{103}Pd in the ranges (1.00, 1.20, 1.45) and (1.00, 1.20, 1.60, 1.75), respectively. It resulted in α/β values between 0.68 Gy (95% CI 0.57, 0.79) and 1.81 Gy (95% CI 1.51, 2.15), considering only estimates with positive values of $T_{1/2}$.

To estimate the sensitivity of the α/β ratio to dose heterogeneities resulting from ^{125}I implants as well as to a set of radiobiological parameters, Lindsay *et al.*[41] equated the tumor control probabilities (TCPs) of EBRT and LDRBT for different values of α,[56] T_{pot},[6,7] RBE,[53,55] and total dose of EBRT treatments. They concluded that, without taking into account dose heterogeneity and interpatient variation, the actual value of α/β is most likely underestimated and could be up to 12 Gy. Increasing RBE or T_{pot} values yielded to a decrease in the α/β ratio. The largest variation occurred for changes in the RBE. In average, changes of RBE between 1.0 and 1.4 yielded a 7.2 Gy decrease in fitted α/β.

Wang *et al.*[15] claimed that other investigators[9–12,40] have not only ignored the problem of the unrealistic clonogenic number (extremely low α values) but also neglected the effect of repopulation of clonogenic cells in RT treatments. They argued that if T_{pot} has a median of 42 days,[7] repopulation would play a role in LDRBT treatments, such as ^{125}I implants which treatment duration is protracted to more than 200 days. The generalized LQ model was applied to the clinical data compiled by Fowler *et al.*[11] and a new clinical dataset of EBRT (Ref. 57) taking into consideration the effects of dose-rate, sublethal damage repair, and clonogenic proliferation. An α/β of 3.1 ± 0.5 Gy was derived.[15] They also solved the problem of the extremely low radiosensitivity and unrealistic clonogen cell number with an α parameter of 0.15 ± 0.04 Gy^{-1} and a clonogenic cell number ranging from 10^6 to 10^7, depending on the patient risk level.

Kal and Van Gellekom[17] also took into account the influence of repopulation and added as a new factor the contribution of edema resulting from the insertion of radioactive seeds in the prostate. This edema has the effect of reducing the dose-rate and, therefore, the physical effective dose and the BED.[58,59] The reanalysis of the clinical data of Fowler *et al.*[11] resulted in an α/β value from 3.1 to 3.9 Gy.

Fowler *et al.*[43] questioned the time delay (T_K) for accelerated proliferation in tumors used by Wang *et al.*[15] and ranging from 0 to 28 days. They argued that if fast proliferating head and neck tumors present a T_K of 21–35 days[60,61] with a T_{pot} from 3.5 to 4.7 days,[62,63] the prostate cancer with a T_{pot} of 42 days,[7] would have a T_K value up to 10 times the T_K for head and neck tumors, approximately between 210 and 300 days. Considering these T_K values, the calculations[9,11] of the α/β ratio of 1.2–1.5 Gy were practically unaltered.

Fowler *et al.*[11] used a generalization of the Brenner and Hall[9] model to determine a $T_{1/2}$ of 1.90 h (95% CI 1.42, 2.86). Using this $T_{1/2}$ and assuming no repopulation, Wang *et al.*[15] derived an α/β of 1.5 Gy, consistent with the result of Fowler *et al.*[11] If, instead, repopulation is considered with a T_{pot} of 42 days, a $T_{1/2}$ of 16 min is obtained, resulting in the reported[15] α/β of 3.1 ± 0.5 Gy. A longer T_{pot} of 62 days yielded a $T_{1/2}$ of 48 min and an α/β of 2.6 Gy. Kal and Van Gellekom[17] found a common $T_{1/2}$ value of 0.5 h for BT and EBRT treatments in the range of the α/β overlap.

Nickers *et al.*[26] used data of 328 patients treated with EBRT and BT boost from either LDRBT or high-dose-rate brachytherapy (HDRBT). The equivalence of dose was established using the incomplete repair model of Dale[64]

TABLE I. Summary of the reported α/β values for prostate cancer.

α/β(Gy)	Source of the data	Assumptions/comments	References
1.5 (95% CI 0.8, 2.2)	FFBF of EBRT + LDRBT	Complete repair after LDRBT No tumor repopulation Biochemical control equivalence of EBRT and LDRBT RBE of permanent implants = 1 Homogeneity of tumor and dose Data collected from different institutions for multiple modalities	9
1.49 (95% CI 1.25, 1.76)	FFBF of EBRT + LDRBT	The same as Brenner and Hall (Ref. 9) except for the use of an exponential repair rate of tumor for LDRBT, μ	11
1.44 (95% CI 1.22, 1.76)	FFBF of EBRT + LDRBT	The same as above	19
~1.8 (^{125}I), ~2 (^{103}Pd)	No fit to data	The same as Brenner and Hall (Ref. 9) but with no fit to clinical data	12
4.96 (95% CI 4.1, 5.6)	FFBF of EBRT + LDRBT	The same as Brenner and Hall (Ref. 9) except for the use of an α represented by a distribution of values	40
2.1	FFBF of EBRT + LDRBT	The same as Brenner and Hall (Ref. 9) except for the use of α and β represented by independent distributions of values	10
0.68 (95% CI 0.57, 0.79) to 1.81 (95% CI 1.51, 2.15)	FFBF of EBRT + LDRBT	The same as Fowler *et al.* (Ref. 11) except for the RBE of permanent implants: RBE (^{125}I) = (1.00, 1.20, 1.45), RBE (^{103}Pd) = (1.00, 1.20, 1.60, 1.75)	14
Nominal parameter values: 2.1–12.3 (all DVHs) 2.1–3.8 (better implants) 1.0–1.8 (uniform doses) Ranges of parameter values: 1.1–12.3 (better implants) 0.7–6.3 (uniform doses)	LDRBT DVHs: Uniform doses of 120, 144 or 160 Gy; four clinical preimplant; four clinical postimplant	Exponential repair rate of tumor, $\mu = 0.693\ \mathrm{h}^{-1}$ TCP (EBRT) = TCP (LDRBT) Nominal parameter values: RBE = 1.4, $T_{pot} = 45$ d, $\alpha = 0.2\ \mathrm{Gy}^{-1}$, D (EBRT) = 70 Gy Ranges of parameter values: RBE = 1.2–1.6, T_{pot} = 25–65 d, α = 0.05–0.3 Gy^{-1}, D (EBRT) = 66–80 Gy	41
3.1 ± 0.5	FFBF of EBRT + LDRBT	The same as Fowler *et al.* (Ref. 11) except for the tumor repopulation starting at $T_k = 0$ or 28 d, $T_{pot} = 42$ d	15
3.1–3.9	FFBF of EBRT + LDRBT	The same as Wang *et al.* (Ref. 15) except for Exponential repair rate of tumor for LDBT, μ = 1.386, 0.693, 0.347 h^{-1} Edema resulting from the insertion of the radioactive seeds, $R_0 = 1.09$ and $\lambda_{edema} = 0.0032\ \mathrm{h}^{-1}$	17
3.41 (95% CI 2.56, 4.26) ($T_{1/2}$ = 1.9 h) 5.87 (95% CI 4.67, 7.07) ($T_{1/2}$ = 1.5 h)	FFBF of EBRT + LDRBT or HDRBT boost	Exponential repair rate of tumor for LDBT, μ = 0.462, 0.365 h^{-1} BED equivalence of EBRT + LDRBT boost and EBRT + HDRBT boost (α/β = 3 Gy) RBE of permanent implants = 1 Homogeneity of dose Use of data from matching rather than from randomized controlled trial	15
Nominal parameter values: >30 (95% CI 5.2, >50) Ranges of parameter values: >30 (95% CI 0.6 –6.5, >50)	FFBF of EBRT + LDRBT	Nominal parameter values: RBE = 1, T_{pot} = 45 d, $T_{1/2}$ = 1 h Ranges of parameter values: RBE = 1–2.0, T_{pot} = 30–90 d, $T_{1/2}$ = 0.5–2 h Homogeneity of dose Use of data from matching rather than from randomized controlled trial	15
1.2 (95% CI 0.03, 4.1)	FFBF of EBRT + HDRBT boost	Complete repair after HDRBT Homogeneity of dose Use of data from matching rather than from randomized controlled trial Short follow-up Small sample size	13
3.1 (68% CI 1.5, 5.7)	FFBF of EBRT + HDRBT boost and EBRT alone	Exponential repair rate of tumor for HDRBT (Ref. 15), μ = 2.599 h^{-1} Clonogen number (Ref. 15), $K = 1.6 \times 10^6$–1.1×10^7 Homogeneity of dose	16
3.7 (95% CI 1.1,∞) (EBRT) 2.6 (95% CI 0.9, 4.8) (EBRT + HDRBT)	FFBF of EBRT + HDRBT boost and EBRT alone	Equivalence of EBRT and HDRBT in terms of dose and dose-rate effects Data collected from different institutions for multiple modalities	23

TABLE I. (*Continued*)

α/β(Gy)	Source of the data	Assumptions/comments	References
4.5 (95% CI 1.6, 8.7) (EBRT + 120% HDRBT increase)			
1.55 (95% CI 0.46, 4.52)	FFBF of EBRT	Data collected from different institutions	27
1.4 (95% CI 0.9, 2.2)	FFBF of EBRT (standard + hypofractionation)	Data collected from different institutions	25
1.86 (95%CI 0.7, 5.1)	FFBF of EBRT (standard + hypofractionation)	No tumor repopulation	28
2.1 Gy	FFBF of EBRT (standard + hypofractionation)	Tumor repopulation by 1 week with dose equivalent of proliferation of 0.25 Gy/d (Ref. 130)	28
8.5 (well-oxygenated clonogens) 50.3 (hypoxic clonogens)	Radiosensitivity parameters from prostate tumor cell lines	Hypoxic microenvironment in prostate tumor, $OER_{\alpha} = 1.75$ and $OER_{\beta} = 13.25$ Interpatient heterogeneity of intrinsic radiosensitivity, σ_{α} β-component contributes insignificantly for the total cell killing Average values of α and β from prostate tumor cell lines, $\alpha = 0.26 \pm 0.06$ Gy^{-1} and $\beta = 0.0312 \pm 0.0064$ Gy^{-2} Complete repair after LDRBT Clonogen number, $K = 5 \times 10^6$ (for LDRBT) and $K = 10^6$ to 10^7(for EBRT) Different details of the several experimental protocols No correction for dose-rate effects	42,71
3.3 (68% CI 1.9, 5.8)[a]	Radiosensitivity parameters from prostate tumor cell lines	Different details of the several experimental protocols Correction for dose-rate effects, G computed with $T_{1/2} = 0.01$ (LNCaP), 8.4 (PPC-1), 8.9 (TSU-Pr1), 5.7 (DU-145), 6.6 (PC-3) h for survival data for several dose rates and $T_{1/2} = 2$ h for survival data for only HDR exposure	18,75
1.12 (95% CI –3.3, 5.6)	FFBF of EBRT randomized trial comparing two different schedules (Ref. 48) (20 F × 2.62 Gy vs 33 F × 2 Gy)	The steepness of the dose–response relationship for a fixed fraction size is known No effect of increasing overall time from 4 to 6.5 weeks on tumor control	20
0.65 (95% CI −1.4, 2.8)	FFBF of EBRT randomized trial comparing two different schedules (20 F × 2.75 Gy vs 32 F × 2 Gy)	The same as above	22
8.3 (95% CI 0.7, 16)	FFBF of EBRT prospective nonrandomized trial comparing two different schedules (Ref. 76) (daily 35–38 F × 2 Gy vs 2 × daily 58–69 F × 1.2 Gy)	Assume $\alpha/\beta = 10$ Gy for isoeffectiveness of the two regimens The steepness of the dose–response relationship for a fixed fraction size is known The outcome after hyperfractionated treatments can be influenced by incomplete repair	20

Note: CI = confidence interval; FFBF = freedom from biochemical failure; EBRT = external-beam radiotherapy; LDRBT = low-dose-rate brachytherapy; RBE = relative biological effectiveness; DVH = dose-volume histogram; TCP = tumor control probability; $T_{1/2}$ = half-time of repair; T_{pot} = potential doubling time; D = prescribed total dose; T_k = time after the starting of treatment at which repopulation begins; BED = biological effective dose; HDRBT = high-dose-rate brachytherapy; OER = oxygen enhancement ratio; G = Lea–Catcheside dose-protraction factor.
[a]For details on reported parameters see Table II.

assuming[15] an α/β of 3 Gy and a $T_{1/2}$ of 1.5 h. Equivalence on biochemical control between the two groups was accessed and confirmed via a Cox proportional hazards analysis consistent with the fitted parameters. Data fitted well an α/β of 3.41 Gy (95% CI 2.56, 4.26) and a $T_{1/2}$ (Ref. 11) of 1.9 h, and also an α/β of 5.87 Gy (95% CI 4.67, 7.07) for a $T_{1/2}$ of 1.5 h. The α/β result did not vary with the three different prognostic groups of prostate cancer.

Shaffer *et al.*[44] estimated the α/β value for low and low-intermediate risk prostate cancer patients treated with EBRT or LDRBT. Patients were matched for the same outcome-associated risk factors and follow-up time. The LQ formulation including the repopulation factor was used to find the best fitting-values of α/β considering RBE = 1, $T_{pot} = 45$ d, and $T_{1/2} = 1$ h. This fit yielded an α/β value higher than 30 Gy with a lower confidence limit of 5.2 Gy. Varying parameters to extreme values, the α/β best-fit was still higher than 30 Gy with a minimum lower confidence limit of 0.6 Gy for RBE = 2, $T_{pot} = 45$ d, and $T_{1/2} = 1$ h, and a maximum of 6.5 Gy for RBE = 1, $T_{pot} = 30$ d, and $T_{1/2} = 0.5$ h.

V. THE CONTRIBUTION OF HDRBT BOOSTS

Interposing previous results, D'Souza and Thames[46] questioned the equivalence of clinical outcomes of EBRT and LDRBT treatments regarding the tumor control definition and prescribed dose. In order to overcome the inherent uncertainties of combining different datasets of LDRBT and EBRT (different dose distributions and specifications, derivation of data from different institutions yielding potential differences in responses to staging and scoring, and possible differences in RBEs of permanent implants), Brenner *et al.*[13] analyzed outcomes from EBRT treatments plus HDRBT boosts reported by Martinez *et al.*[65] In the HDRBT protocol, treatment was delivered in two or three implants of ^{192}Ir escalated from 5.5 to 6.5 Gy (three implants) and from 8.25 to 10.5 Gy (two implants). Analysis was performed using standard models of tumor cure based on Poisson statistics combined with the LQ formalism. The authors found an α/β value of 1.2 Gy (95% CI 0.03, 4.1) which they claimed consistent with previous estimations.

One year later, Wang *et al.*[16] reanalyzed the data from Martinez *et al.*[65,66] with a longer follow-up, allowing for maturity and stability in the data and a new clinical dataset[57,67] from EBRT dose-escalation to determine the standard uncertainties of parameters. Using the same formalism as before,[15] an α/β ratio of 3.1 Gy (68% CI 1.5, 5.7) was reported by these authors.

To avoid dose inhomogeneity, Williams *et al.*[23] made an attempt to estimate the prostate cancer α/β ratio by considering only EBRT data of a total of 3756 patients with a range of fraction sizes. The α/β ratios were estimated via a proportional hazards model stratified by risk severity and institution. Using biochemical failure as an endpoint resulted in an α/β estimate of 3.7 Gy (95% CI 1.1, ∞). Despite the large sample size and fractionation schedules, the use of EBRT data alone showed a high level of uncertainty, although the tendency for low α/β values. Incorporating in the analysis a small number of HDRBT boost patients (185 patients), the precision of the estimation was improved to 2.6 Gy (95% CI 0.9, 4.8). To access the sensitivity of the previous estimation to the addition of the HDRBT data, authors also assumed that the effective tumor dose for each high-dose-rate fraction was higher than the prescribed dose. With a 20% increment in the fraction dose, the α/β ratio increased to 4.5 Gy (95% CI 1.6, 8.7).

VI. THE USE OF EBRT DATA ALONE

To overcome the large uncertainties found in Williams *et al.*[23] estimation of the α/β ratio by using only EBRT data, Proust-Lima *et al.*[27] avoided to use the conventional binary failure endpoint to access outcome by incorporating a multivariable modeling approach focused on the prostate-specific antigen (PSA) values after treatment. PSA measures were accessed in a total of 5093 patients with localized prostate cancer treated with EBRT. The total dose of EBRT and the sum of square doses-per-fraction were associated with long-term PSA rise. An estimate of 1.55 Gy (95% CI 0.46, 4.52) was obtained with this approach.

Miralbell *et al.*[24,25] collected data from 5969 patients treated with EBRT standard fractionation (40%) and hypofractionation (60%) with 2.7–6.7 Gy per fraction. Primary endpoint was biochemical no evidence of disease (bNED) using Phoenix definition. The value of the estimated α/β ratio was 1.4 Gy (95% CI 0.9, 2.2). No major differences were found in the α/β value for the different risk groups.

Leborgne *et al.*[28] reported a low α/β derived from the outcome of patients treated with hypofractionated EBRT delivered in 3.0–3.15 Gy fractions and patients treated with standard fractionation. The parameter value which better matched the actuarial bNED at 5 years was 1.86 Gy (95% CI 0.7, 5.1).

VII. THE INFLUENCE OF HYPOXIA

Nahum *et al.*[42] proposed a model of prostate cancer response to ionizing radiation by applying biological factors which may influence the intrinsic radiosensitivity of the aerobic tumor clonogens. A model of TCP incorporating both interpatient variation of intrinsic radiosensitivity and the effect of hypoxia was used together with average values of radiosensitivity (α and β) published for prostate cancer cell lines (see Table II and Table I from Nahum *et al.*[42]). To account for hypoxia, oxygen enhancement ratio (OER) factors of 1.75 and 3.25 were used for α and β-inactivation, respectively.[68,69] An α/β ratio of 8.5 Gy was derived for well-oxygenated cells and of 15.5 Gy for hypoxic cells. Orton[70] commented on Nahum *et al.*[42] results claiming that these authors used an incorrect value of β for hypoxic cells. The correction of this parameter resulted in a much higher α/β ratio of 50.3 Gy for hypoxic cells.[71] The report of Nahum *et al.*[42] was also criticized by Wang *et al.*[47] who, among other factors, objected about the relevance and reliability of the *in vitro* data. In disagreement with the relation between the decreased radiosensitivity due to hypoxia and the α/β ratio, Fowler[33] referred that its significance with respect to the α/β values is unknown and speculated that hypoxia might slow down proliferation leading to a decrease in the α/β value. On the other hand, Carlson *et al.*[18] claimed that Nahum *et al.*[42] made no attempt to correct for dose-rate effects and that radiosensitivity parameters of PC3 cell line from Leith *et al.*[72] were incorrectly reported. The reanalysis of Carlson *et al.*[18] of the *in vitro* data suggested that the α/β ratios reported by Nahum *et al.*[42] were too high (see Sec. VIII).

VIII. THE CONTRIBUTION OF THE *IN VITRO* STUDIES

Table II summarizes *in vitro* survival data for six cell lines.[72–74] Reported α/β ratios are between 1.2 and 34.0 Gy. If removing the data from LnCap cell line which yields the highest α/β values, reminder will lie between 1.2 and 8.8 Gy which are within the range of the clinical derived values. Carlson *et al.*[18] reanalyzed survival data[72–74] for the six prostate cancer cell lines presented in Table II in a total of 10 datasets using LQ survival model. Paired bootstrap for regression was used to compute 95% confidence intervals. Attempt was made to correct for dose-rate effects. Estimates[75] of α/β ranged from 1.1 to 6.29 Gy, with a geometric mean of 3.3 Gy and corresponding standard deviation (SD) of 1.9–5.8 Gy. These investigators concluded that estimates of the α/β ratio derived from *in vitro* and clinical data are consistent with an α/β ratio less than about 3–4 Gy.

TABLE II. α and β-coefficients reported for six human prostate cancer cell lines.

Cell line	α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)	References	α/β (Gy) Reported[a] by Carlson (Ref. 18)
PC-3	0.487	0.055	8.8	72	4.93 (95% CI 3.17, 7.51)
	0.241	0.069	3.5	73	3.09 (95% CI 2.22, 4.15)
	0.064	0.017	3.7	74	4.11 (95% CI 2.51, 5.72)
DU-145	0.155	0.0521	2.9	72	3.11 (95% CI 2.33, 3.36)
	0.099	0.009	11	74	6.29 (95% CI 4.09, 9.74)
	0.313	0.048	6.5	73	5.71 (95% CI 2.90, 15.51)
LnCaP	0.29	0.013	22.3	74	1.09 (95% CI 1.06, 1.36)
PPC-1	0.1	0.026	3.8	74	2.49 (95% CI 1.89, 3.05)
TSU-Pr1	0.115	0.015	7.7	74	4.72 (95% CI 2.42, 10.69)
TSU	0.062	0.05	1.2	73	1.80 (95% CI 0.65, 3.42)

[a]Best estimates of α/β derived from the reanalyses of the published data reported by Carlson *et al.* (Ref. 18).

IX. ESTIMATIONS FROM HYPERFRACTIONATION RESULTS

Valdagni *et al.*[76] reported on a prospective nonrandomized trial using conventional 2 Gy daily treatments vs 1.2 Gy twice a day. Hyperfractionation reduced late toxicities and yielded a better biochemical control inconsistent with a low α/β ratio. Bentzen and Ritter[20] applied a method to determine the α/β ratio and its 95% confidence interval for two nonisoeffective regimens since the steepness of the dose–-response curve was known. The estimate of the slope of the dose–response curve of Cheung *et al.*[77] was used. The α/β value was calculated from the hazard ratios reported by Valdagni *et al.*[76] resulting in an estimate of 8.3 Gy (95% CI 0.7, 16). Bentzen and Ritter[20] claimed that this confidence interval cannot exclude the low values of α/β and suggested that the hypofractionated schedule might suffer from incomplete repair.

X. ESTIMATIONS FROM HYPOFRACTIONATION RANDOMIZED TRIALS

Lukka *et al.*[48,78] randomized 936 patients treated with 20 fractions of 2.62 Gy (short arm) vs 33 fractions of 2 Gy (long arm) of EBRT. At 5-year follow-up, biochemical or clinical failure probability was higher in the short arm (60%) compared with the long arm (53%), although the total hypofractionated dose was too low to give equality with the controlled arm.[33] There were no differences in the overall survival or in late toxicity. Applying the same method as for the Valdagni *et al.*[76] trial in combination with the hazard ratio and its 95% confidence limits to the Lukka *et al.*[48] results yielded an α/β of 1.12 Gy (95% CI −3.3, 5.6).

Another randomized trial on hypofractionation was performed by Yeoh *et al.*[21,22,79] in which hypofractionated schedules of 20 fractions of 2.75 Gy were compared with regimens of 32 fractions of 2 Gy for a total of 217 patients. At 90 months follow-up, biochemical relapse-free survival for the hypofractionated and conventional groups was 53% and 44% using the Phoenix criteria, respectively.[22] The estimation of the α/β ratio was, as previous, made upon the slope of the prostate cancer dose–response curve resulting in a value of 2.2 Gy (95% CI −6.0, 10.6) from Yeoh *et al.*,[21] with a median follow-up of 48 months and 0.65 Gy (95% CI −1.4, 2.8) with the updated results of Yeoh *et al.*[22] at 90 months follow-up. Both datasets[21,48] exemplify the problem of identifying α/β values within clinical relevant 95% confidence intervals, although the considerable reduction in the interval width with the longer follow-up results of Yoeh[22] trial. Also, the estimations of Bentzen and Ritter[20] and Yeoh *et al.*[21,22] assume that the dose–response relationship for a fixed fraction size is known and do not take into account the effect of increasing the overall time from 4 weeks with the hypofractionated schedules to 6.5 weeks with the conventional fractionated regimens.

Pollack *et al.*[80,81] randomized 303 patients of intermediate and high risk prostate cancer treated with 26 fractions of 2.7 Gy or 38 fractions of 2 Gy. The rational for the design of the hypofractionated schedule was based on the potential therapeutic gain assuming an α/β ratio of 1.5 Gy. Investigators reported no differences between the two regimens in relation to patient outcome or toxicity at a median follow-up of 39 months. They also concluded that if no difference exists between the two arms with longer follow-up, the α/β ratio could be above 3 (possibly 6.5 or even higher).

XI. FEASIBILITY OF THE HYPOFRACTIONATION REGIMENS

Clinical studies of hypofractionated treatments of prostate cancer have shown that this modality is safe and effective. Nonrandomized studies of moderately hypofractionated EBRT (2.5–4 Gy fractions) delivered mainly by intensity-modulated radiotherapy (IMRT) or 3D-conformal radiotherapy have reported biochemical outcomes comparable with that achieved with conventional fractionated RT (Refs. 82–92) and with limited rectal and bladder late complications.[82–95] Reported median follow-up time varied from 19 to 51 months. Publications on prostate cancer patients treated with conventional fractionated EBRT combined with hypofractionated IMRT boosts[96] of 2 fractions of 5-8 Gy (median follow-up of 63 months) or with concomitant boosts[97,98] in 28 fractions of 2.5 Gy and 25 fractions of 2.7 Gy (median follow-up of 46 and 39 months, respectively) concluded that these treatments were feasible and well tolerated. The results on EBRT treatments in combination with HDRBT boosts[65,66,99–105] with median follow-up ranging from 40 to 105 months (2 fractions $\times$ 5–15 Gy, 3 fractions $\times$ 3–6.5 Gy, or 4 fractions $\times$ 3–6 Gy) and extreme hypofractionated treatments of HDRBT delivered as monotherapy[106–112] at median follow-up of 22–65 months (3 fractions $\times$ 10.5 Gy, 4 fractions $\times$ 8.5–9.5 Gy, 6 fractions $\times$ 6.75–7 Gy, 8 fractions $\times$ 6 Gy, or 9 fractions $\times$ 6 Gy) or stereotactic body radiosurgery[113–115] with median follow-up varying from 33 to 60 months (5 fractions $\times$ 6.7–7.25 Gy) have been revealing high rates of biochemical control associated with low morbidity. Analysis of the results of hypofractionated conformal carbon ion RT (Ref. 116) delivered in 20 fractions of 3.3 Gy also yielded satisfactory biochemical control and minimal morbidity at median follow-up of 30 months. On the other hand, if some recent studies have reported equivalence in biochemical outcome and/or complication rates when comparing 26 fractions of 2.7 Gy with 38 fractions of 2 Gy (Pollack *et al.*,[81] median follow-up: 39 months; Turaka *et al.*,[117] median follow-up: 55 months) or 30 fractions of 2.4 Gy with 42 fractions of 1.8 Gy (Kuban *et al.*,[118] median follow-up: 58 months for the hypofractionation regimens and 55 months for the conventional), others revealed equivalence in late toxicity with superior outcome in the hypofractionated schedule as delivered in 20 fractions of 3.1 Gy vs 40 fractions of 2 Gy (Arcangeli *et al.*,[119,120] median follow-up: 32 months for the hypofractionation regimens and 35 months for the conventional). Despite differences in dose prescription, delivery methods, patient selection according to prognostic factors, short follow-up in many studies, and the use of androgen deprivation therapy in some patients, the clinical experience with hypofractionation seems to be consistent with a low α/β ratio for prostate cancer.

XII. THE α/β VALUE FOR PROSTATE CANCER

Five years ago, in 2007, a review of the α/β values reported to that date was published by Daşu.[37] However, several reports were published ever since with new estimations for the prostate cancer α/β.[22,23,25–28,44] Similarly, several studies comparing the biochemical outcome and late toxicity in patients treated with hypofractionation and conventional regimens are now available, showing the feasibility of hypofractionation used to treat prostate cancer by radiation.[22,24,25,28,48–52] Although the first estimations from randomized trials have drawn the idea of a low α/β value for prostate cancer,[20,21] the associated large width of the 95% confidence intervals indicated a considerable uncertainty related with such evaluations. Now, datasets reflecting longer follow-up allowed to substantially reduce these margins.[22] For example, Yeoh *et al.*[21] reported a value of 2.2 Gy (95% CI -6.0, 10.6) in 2006 at 48 months follow-up which was reduced to 0.65 Gy (95% CI -1.4, 2.8) with a longer follow-up of 90 months in 2011;[22] Miralbell *et al.*,[25] in 2012, found a value of 1.4 Gy (95% CI 0.9, 2.2) through the assembly of seven different datasets in a total of 5969 patients with a median follow-up of 41 months in 40 patients, 52 months in 403, and more than 60 months in the remaining.

Figure 1 shows a summary of the reported α/β values published with the corresponding 95% CI limits. Studies reported after the review of Daşu[37] are highlighted with the references in bold. An arithmetic mean of all these reports yielded an α/β average of 2.73 Gy with a SD of 1.96 Gy. Figure 2 was built upon the values represented in Fig. 1 and shows also the arithmetic mean of the α/β values reported before 2007 (2.88 Gy, SD = 2.15 Gy) and in the year of 2007 and after (2.48 Gy, SD = 1.74 Gy). Moreover, the corresponding arithmetic mean of the 95% CI amplitudes and its SD are also represented in Fig. 2. A clear reduction not only in these intervals but also in its variation can be observed from studies reported before 2007 (5.57 Gy, SD = 4.99 Gy) to the more recent reports (3.14 Gy, SD = 1.30 Gy). An average amplitude of 4.62 Gy with a SD of 4.09 Gy was obtained when considering all the studies. Therefore, although the averaged reported values for the α/β ratio of prostate cancer have not considerably changed since the time of the last review, the amplitude of the reported CI decreased considerably, increasing the confidence on its value.

XIII. FINAL CONSIDERATIONS

Although clinical practice of hypofractionation in the treatment of prostate cancer seems not to increase late

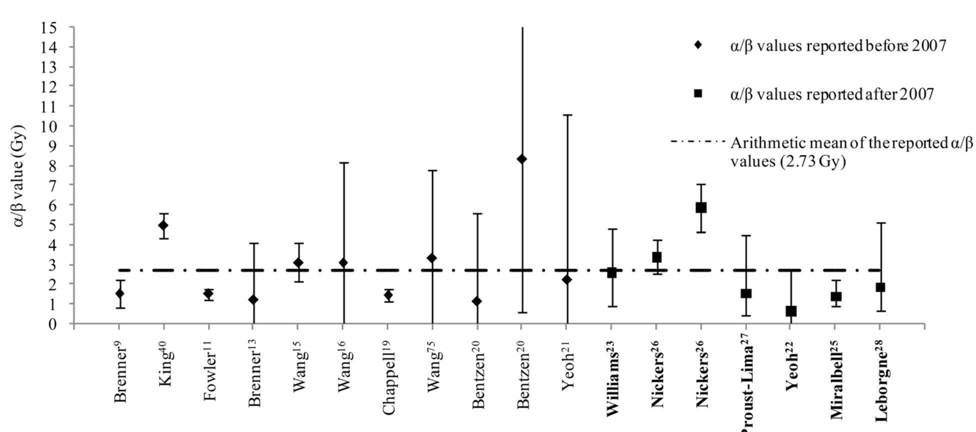

FIG. 1. Summary of reported α/β values and the corresponding 95% CI adapted from Daşu (Ref. 37) Published values without defined CI are not shown. Square points and references in bold are those published after Daşu (Ref. 37) review.The dashed–dotted line represents the arithmetic mean of the α/βvalues (2.73 Gy).

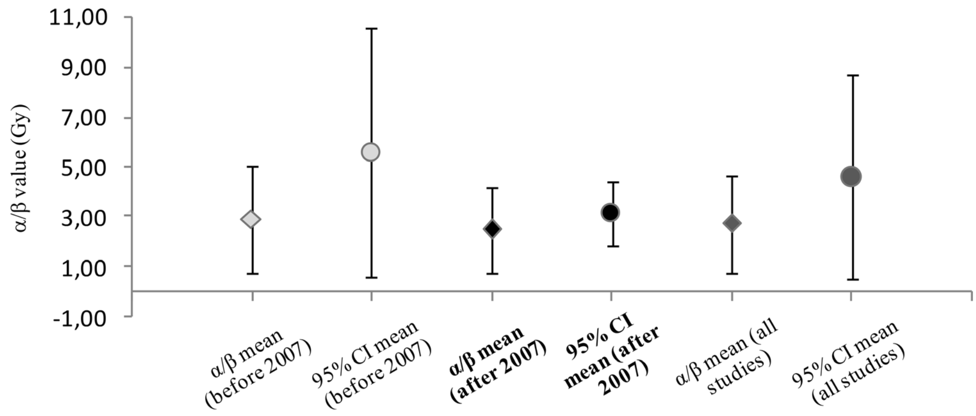

FIG. 2. Arithmetic mean and corresponding SD of the reported α/β values shown in Fig. 1 before (lozenge light gray points: 2.88 Gy, SD = 2.15 Gy) and after Daşu (Ref. 37) review (lozenge black points: 2.48 Gy, SD = 1.74 Gy) and from all studies (lozenge dark gray: 2.73 Gy, SD = 1.96 Gy). The arithmetic mean of the 95% CI amplitudes of those studies is also represented with the corresponding SD before 2007 (circle light gray points 5.57 Gy, SD = 4.99 Gy), after 2007 (circle black points: 3.14 Gy, SD = 1.30 Gy) and from all the reports (circle dark gray: 4.62 Gy, SD = 4.09).

complication and shows a biochemical outcome superior or equivalent to conventional schedules, caution must be taken when using extreme hypofractionated schedules (less than ten fractions) due to the negative effects of hypoxia on cell killing by radiation.[121] In prostate cancer, fractional hypoxic values were found to be between 0% and 94% with a median of 18% using positron emission tomography scans and the hypoxia-binding [^{18}F]fluoromisonidazole.[122] Estimations of hypoxic fractions from cell survival curves of xenografted human tumors[72] derived hypoxic fractions of 7% and 52% for DU-145 and PC-3 tumors, respectively. *In vivo* measurements of pO_2 using Eppendorf microelectrodes[123] revealed lower pO_2 in the pathological involved side of the prostate compared with normal muscle, suggesting that hypoxic regions exist in human prostate cancer. Increasing levels of hypoxia were correlated with increasing clinical stage[124] and early biochemical failure.[125] Parker *et al.*[126] measured the intraprostatic oxygen tension using Eppendorf electrodes and confirmed that hypoxia exists in prostate cancer but found no association between oxygen values and clinical prognostic factors or differences between oxygenation of tumor regions and normal prostate. Furthermore, Carlson *et al.*[121] found that tumor cell survival increases by a factor of $\sim 4 \times 10^2$ as the dose per fraction is increased from 2.0 Gy (n = 40) to 18 Gy (n = 1) for prostate cancer which authors attributed to possible changes in the α/β ratio with heterogeneous oxygenation, reduction in interfraction reoxygenation, and an increased importance of the hypoxic fraction in determining dose responses with the use of higher doses per fraction. Nahum *et al.*[42] reported an increased α/β value for more radioresistent hypoxic tumors, comparing to well-oxygenated tumor cells, although recent estimations did not find a correlation between the α/β ratio and different risk groups of prostate cancer.[24–27]

Another factor that may influence the α/β estimations when using LDRBT clinical data is the onset of tumor cells repopulation after the beginning of treatment. Brenner and Hall[9] and Fowler *et al.*[11] neglected repopulation during the radiation treatment and produced an α/β of $\sim$1.5 Gy. On the other hand, Wang *et al.*[15] and Kal and Van Gellekom,[17] considering a repopulation onset of 0 or 28 days after the beginning of the treatment, reported α/β values of $\sim$3.1–3.9 Gy which would fall into the previous values[15] if repopulation was not considered. Despite the data indicating that overall treatment time could be protracted by, at least, 9 weeks without evident impact in outcome,[127] some recent studies have reported that prolongation of treatment in patients with T2 localized prostate cancer for more than 9 weeks may worsen biochemical outcome.[128] Likewise, breaks of more than 3 days in a 38-fraction treatment or of more than 4 days in a 40-fraction in low risk patients should be avoided.[129] A relative increase of 6% in biochemical failures was found when the treatment time was elapsed for 1 week (total of 7 weeks) in low- and intermediate risk patients.[130] Leborgne *et al.*,[28] regarding these last results,[130] considered a T_K of 52 days and a proliferation rate of 0.25 Gy/d which yielded a slight increment in the α/β from 1.86 Gy (assuming no proliferation) up to 2.1 Gy. More studies are needed to understand the role of repopulation on prostate cancer treatment by radiation and what is its real impact on the α/β value. RBE of permanent implants may also influence the α/β estimations from LDRBT data.[14,41,44,45] The correction for this factor yielded lower values for the α/β ratio.

The introduction of the half-time of repair in Fowler *et al.*[11] study did not have a substantial impact in the α/β estimation regarding the previous finding of Brenner and Hall.[9] However, Nickers *et al.*[26] found an increase of more than 2 Gy when decreasing $T_{1/2}$ from 1.9 to 1.5 h. These authors attributed this variation as well as the large confidence interval to the diversity of the LDRBT patients' data and to the interpatient heterogeneity of tumors. In fact, the tumor heterogeneity may increase the actual α/β value,[42,131] and the use of homogeneous models overestimates its statistical significance.[132]

If some studies suggest some correlation between *in vitro* and *in vivo* parameters,[133–141] in others little or no correspondence is achieved between *in vitro* predictions and relevant clinical endpoints.[141–146] This lack of correlation may be due to small patient sample sizes, unreliable radiosensitivity indicators, or uncertain relationship among *in vitro* indicators and *in vivo* endpoints.[18] Nonetheless, a review of the *in vitro* data of prostate cancer cell lines performed by Carlson *et al*.[18] resulted in an α/β geometric mean of 3.3 Gy that agrees with other clinical estimations that took into account the repopulation factor despite the large confidence intervals reported.[75]

At date, evidence mounts that the α/β ratio for prostate cancer is low, around 2.7 Gy. Since the last review of the prostate cancer α/β performed by Daşu,[37] several other reports have been published providing new estimations of the α/β value and re-enforcing the idea that it might be low. Also, the reported amplitudes of the CI considerably decreased, increasing the reliability of the most recent studies. Considering that this value is lower than that for late rectal complications,[147] with an α/β of 5.4 ± 1.5 Gy, a therapeutic gain may be achieved when using hypofractionation protocols. However, one cannot forget all the uncertainties that have been revealed around the α/β estimation and we expect that, with the maturation of the ongoing randomized trials, a more precise answer could be achieved in a recent future. Also, the use of extreme hypofractionated treatments should be evaluated carefully due to the possible reduction on biochemical outcome triggered by other radiobiological factors such as hypoxia. Acute toxicity may also increase with the hypofractionated regimens,[78,80,148,149] possibly due to a higher net of stem-cell depletion in the rectal and bladder mucosa.[78]

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