e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2021, Volume 26, Number 5, pages: 664–673
DOI: 10.5603/RPOR.a2021.0081
Submitted: 28.09.2020
Accepted: 28.02.2021

Heuristic estimation of the α/β ratio for a cohort of Mexican patients with prostate cancer treated with external radiotherapy techniques

Christian S. Adame González[1, 3], José Trinidad Álvarez Romero[2], Mario Moranchel y Rodríguez[3], Armando Félix Leyva[4], Michelle Aline Villavicencio Queijeiro[5], María Yicel Bautista Hernández[6]

[1]Departamento de Física Médica, Centro Médico Nacional 20 de Noviembre, Ciudad de México, Mexico
[2]LSCD, Instituto Nacional de Investigaciones Nucleares, La Marquesa, Ocoyoacac, México
[3]Instituto Politécnico Nacional, Escuela Superior de Física y Matemáticas, Ciudad de México, Mexico
[4]Departamento de Radioterapia, Hospital de Oncología, Centro Médico Nacional, Siglo XXI, Ciudad de México, Mexico
[5]Departamento de Radioterapia, Centro Médico Nacional 20 de Noviembre, Ciudad de México, Mexico
[6]Departamento de Radioterapia, Hospital General de México, Dr. Eduardo Liceaga, Ciudad de México, Mexico

ABSTRACT

Background: The aim of the study was to Estimate and compare the radiobiological ratio α/β with the heuristic method for a cohort of Mexican patients with prostate cancer (PCa) who were treated with external radiotherapy (RT) techniques at three Hospital Institutions in Mexico City. With the Kaplan-Meier technique and the Cox proportional hazards model, the biochemical relapse-free survival (bRFS) is determined and characterized for cohorts of Mexican patients with PCa who received treatment with external RT. Using these clinical outcomes, the radiobiological parameter α/β is determined using the heuristic methodology of Pedicini et. al.

Materials and methods: The α/β is calculated from the survival curves for different treatment schemes implemented at three distinct hospitals. The Pedicini's techniques allow to determine the parameters α/β, k and N_0 when treatments are not radiobiologically equivalent, therefore, are built up of a set of curved pairs for the biologically effective dose (BED) versus the ratio α/β, where the ratio is given by the intersection for each pair of curves.

Results: Six different values of α/β were found: the first α/β = 2.46 Gy, the second α/β = 3.30 Gy, the third for α/β = 3.25 Gy, the fourth α/β = 3.24 Gy, the fifth α/β = 3.38 Gy and the last α/β = 4.08 Gy. These values can be explained as follows: a) The bRFS of the schemes presents a statistical variation; b) The absorbed doses given to the patient present uncertainties on the physical dosimetry that are not on the modeling; c) Finally, in the model for the bRFS of Eq. (3), there are parameters that have to be considered, such as: the number of clonogenic tumor cells N_0, the overall treatment time (OTT), the kick-off time for tumor repopulation T_k and the repopulation doubling time. Therefore, the mean value to α/β for all schemes has an average value of 3.29 (± 0.52) Gy.

Conclusions: The value of $\overline{\alpha/\beta}$ = 3.29 (± 0.52) Gy is determined from cohorts of Mexican patients with PCa treated with external radiotherapy using the time-dependent LQ model, which is a higher value with respect to the "dogma" value of α/β 1.5 Gy obtained with the LQ model without temporal dependence. Therefore, there is a possibility of optimizing treatments radiobiologically and improving the results of bRFS in Mexican patients with PCa treated with external radiotherapy.

Key words: α/β ratio; time-dependent LQ model; biochemical relapse-free survival; bRFS; biologically effective dose; BED; prostate cancer, PCa

Rep Pract Oncol Radiother 2021;26(5):664–673

Address for correspondence: Christian S. Adame González, Departamento de Física Médica, Centro Médico Nacional 20 de Noviembre, Av. Félix Cuevas 540, Col. Del Valle, 03229 Ciudad de México; e-mail: christhian.adame@gmail.com

Introduction

Prostate cancer (PCa) is the second most common type of cancer in men in the world. Based on GLOBOCAN estimates, 1,276,106 new cases of PCa were diagnosed worldwide in 2018. In fact, there is a great variety of reported incidence rates of PCa around the world. In Latin America, 190,385 new cases of PCa were reported in the same year, while in Mexico 25,049 patients with PCa emerged. PCa is the second most frequent type of cancer in both regions [2].

Consequently, PCa is a major cause of mortality among men. Worldwide, this type of cancer was the fifth leading cause of death in 2018, with a figure of 358,989 deaths, while in Mexico that figure reached 6,915, which was the leading cause of death from any type of cancer [2].

Several studies report notable differences in the incidence and mortality from PCa amongst the different racial groups. For example, there is a striking disparity in PCa mortality rate among racial groups in the United States, with the highest incidence and mortality seen in African-American men. Deaths attributable to PCa are 2.4 times higher in African-American men compared to white men in the United States [3]. Additionally, PCa incidence and mortality rates are lower among Asian/Pacific Islanders, American Indians/Alaska Natives, and Hispanic men when compared to non-Hispanic white men [3]. Although more studies are needed to explain the causes of these disparities, some of the differences observed between racial groups suggest that genetic factors could play an important role in these inequalities [4]. However, this issue is extremely complex due to its dependence on socioeconomic factors, issues that are beyond the scope of this research.

The RT is one of the main treatment options for PCa. It is well known that there are physical and biological factors that influence the response of tissues from treatment. For example, the uncertainty of the relative and absolute absorbed dose [5], the radiosensitivity, repopulation [1, 6–9], reoxygenation, repair and redistribution [10]. Furthermore, PCa has been characterized as a tissue with slow repopulation and repair, which is expressed with a low value of $\alpha/\beta \sim 1.5$ Gy [11–14], an interpretation that seems to be incorrect, since the low repopulation does not mean that the temporal dependence in the linear quadratic (LQ) model has to be ignored [1].

In PCa where a low α/β value has been assumed as standard, it is considered that hypofractionation schemes can favor cell death and, therefore, a better local control of the disease. However, recent research points to the need to consider the time factor in the calculation of α/β [1, 6–8, 15]. In these scenarios, the tolerances and types of tissues located in the treatment area must be considered very carefully, due to the risks of developing further toxicity, as Ferreira's studies show [16].

In recent years there has been a rapid increase in treatments for PCa with hypofractionated external RT. Even though, there are results in several countries regarding the radiobiological equivalence of PCa treatment schemes (hypo *vs.* standard), it is convenient to determinate and verify the values of the radiobiological parameters for the Mexican male population. With the aim in mind of performing a radiobiological optimization in such treatments for the Mexican population.

The foregoing is of enormous importance, given that these studies are not available in our country, Mexico. As mentioned above, there are notable differences in the incidence and mortality from PCa between ethnic groups, the causes of which are not yet known and deserve further explanation. It is very important to create a national cancer registry with reliable data on incidence rates, tumor type and location, mortality and morbidity allowing us to carry out radiobiological modeling in our Mexican population [17, 18].

To summarize, the aim of this work is to estimate and compare the radiobiological ratio α/β for Mexican patients with PCa who were treated with external RT techniques. The testing took place in three separate hospital institutions located in Mexico City. The RT techniques used in these patients were three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) [19]. The biochemical relapse-free survival (bRFS) values obtained in the study are taken as a reference to perform a radiobiological optimization [19]. These values are also used to determine the α/β for the Mexican population by which the heuristic Pedicini's method is used [20].

Table 1. The biochemical relapse-free survival (bRFS) rates by institution, technique, and treatment scheme from prostate cancer (PCa) Mexican cohort and biologically effective dose (BED) and equivalent dose (EQ2) calculated with α/β = 1.4 Gy

Hospital	No. patients	Technique	Dose fx [Gy]	Total dose [Gy]	EQ_2 [Gy]	BED [Gy]	bRFS rate
IMSS	93	3D-CRT	1.8	70–79	62–70	157–177	94.60%
	80	3D-CRT	2.66	66	77	190	91.30%
	121	SBRT	7	35	90	214	95.90%
	129	SBRT	7.25	36	92	228	89.10%
ISSSTE	57	3D-CRT	1.8–2.0	60–74	58–66	143–165	87.70%
HGM	115	IMRT	1.8	76–79	67–70	169–177	88.70%
Global	595						91.40%

3D-CRT — three-dimensional conformal radiation therapy; SBRT — stereotactic body radiation therapy; IMRT — intensity-modulated radiation therapy

Materials and methods

The bRFS rates are obtained and characterized with the Kaplan-Meier technique for a cohort of Mexican patients (n_{Total} = 595) with PCa who received treatment with external radiotherapy [19], see Table 1. This research confirms that the rates of bRFS are statistically equivalent within the cohort of Mexican patients with respect to the treatments. In other words, the treatments reported in this work are radiobiologically equivalent. By using these clinical outcomes, a set of radiobiological parameters α/β for a Mexican population cohort is determined.

It is worth mentioning that the BED and the equivalent dose (EQ_2) are calculated and reported in Table 1 using the α/β =1.4 given for a Caucasian population [11].

On the other hand, the radiobiological models based on the LQ equation have been widely used over the years to describe the surviving fraction *S* after receiving an absorbed dose *D* [20, 21].

This *S* is expressed as:

$$S = e^{-E} \quad (1)$$

where *E* is the biologically effective yield of lethal damage per cell; moreover, when *E* is corrected for repopulation effect, then it is written as:

$$E = D \cdot (\alpha + \beta \cdot d) + k \cdot (T - T_k) \quad (2)$$

here the radiobiological parameters α and β specify the radiosensitivity of the tumor, while the total absorbed dose delivered is given $D = n \times d$, where *n* is the number of treatment fractions. *T* represents overall treatment time (OTT), T_k is the kick-off time for tumor repopulation and $k = \ln 2/\alpha T_d$ quantifies the rate of tumor repopulation [22]; T_d being the repopulation doubling time. It is to note that, unfortunately, Pedicini defines the γ parameter that corresponds to the *k* parameter of our Eq. (2) incorrectly, as $\gamma = \ln 2/T_d$, see Kahn's Eq. (20.13) [20, 23].

The bRFS for outcomes of radiation treatment is calculated from *S* of Eq. (1), assuming the Poisson distribution as [20]:

$$bRFS = e^{-N_0 \cdot S} \quad (3)$$

where the bRFS for a treatment scheme defined by: *d*, *D* and *T*, is modeled with the K-M technique, see Table 1; and, N_0 is the number of clonogenic cells in the tumor volume, where, unfortunately, some studies do not take care to verify the values of this parameter [11, 20].

On the other hand, the BED is derived directly from the LQ for the cell survival, where the BED is used to calculate and compare treatment schemes that are equally biologically effective [23].

$$BED = d \cdot n \cdot \left(1 + \frac{d}{\alpha/\beta}\right) - k \cdot (T - T_k) \quad (4)$$

here *d* is the absorbed dose per fraction and *n* is the number of fractions reported in Table 1.

Thus, due to the fact that our treatment schemes are radiobiologically equivalent [19], the α/β is determined for the different treatment schemes with the BED calculated with Eq. (4) under the former hypothesis and the assumption that the doubling time T_d = 50 days and an accelerated repopulation time T_k = 30 days, which correspond to *k* = 0.1 Gy/day recommended by Khan [23]. It

should be noted that to uniquely determine the parameter k, it is necessary to calculate α, which we have determined from our data as $\bar{\alpha}$ = 0.130 (± 0.010) Gy.

In fact, we tried to use the values T_d = 5.1 days and T_k = 30 days used by Pedicini; however, it gives us a value of k = 1.20 Gy/day, which is not consistent with the clinical recommendations of Khan [23]. On the other hand, if we take the Vogelius value of 0.31 Gy/day [6], it would correspond to T_d and T_k of 19.4 days and 30 days, respectively, except for the α value that is a free parameter. Because of this, which we have determined as the $\bar{\alpha}$ = 0.130 (± 0.010) Gy; robust criteria or techniques are required to univocally determine the T_d and T_k times consistent with the clinical data of the survival curves.

This heuristic technique consists in obtaining the α/β as the intersection point on the curves BED versus α/β plotted for two treatments that are not necessarily radiobiologically equivalent (that is, they may have statistically different bRFS). In addition, this technique is used for considering heuristically values of T_d, T_k and N_0 that are logically consistent with the observed clinical results. This is unlike other models that estimate inconsistent N_0 parameters and that show a biased time dependence analysys [11].

To summarize and reiterate with pedagogical purposes: the treatment schemes published by Adame et al. are radiobiologically equivalent [19], the α/β's are determined using the reported bRFS's and calculated BED's. with Eq. (4). Therefore, the α/β ratios are obtained from the BED curves as a function of α/β and k, where their values correspond to the point of intersection of the curves [14].

Results

Figure 1 shows 6 different curves for the BED values as a function of α/β's for T_d = 50 days (k = 0.1 Gy/days) y T_k = 30 days corresponding to the external RT treatment schemes used, where six points of intersection are found.

To increase the understanding and precision of the α/β values found, the pairs of curves related to the observed intersection points are presented individually below:

- the first point of intersection has a value α/β = 2.46 Gy, see Figure 2, and is associated with the IMSS-SBRT-HS *vs.* IMSS-3D-HS treatment schemes;
- the second value of α/β is better observed in Figure 3, which corresponds to 3.30 Gy, linked

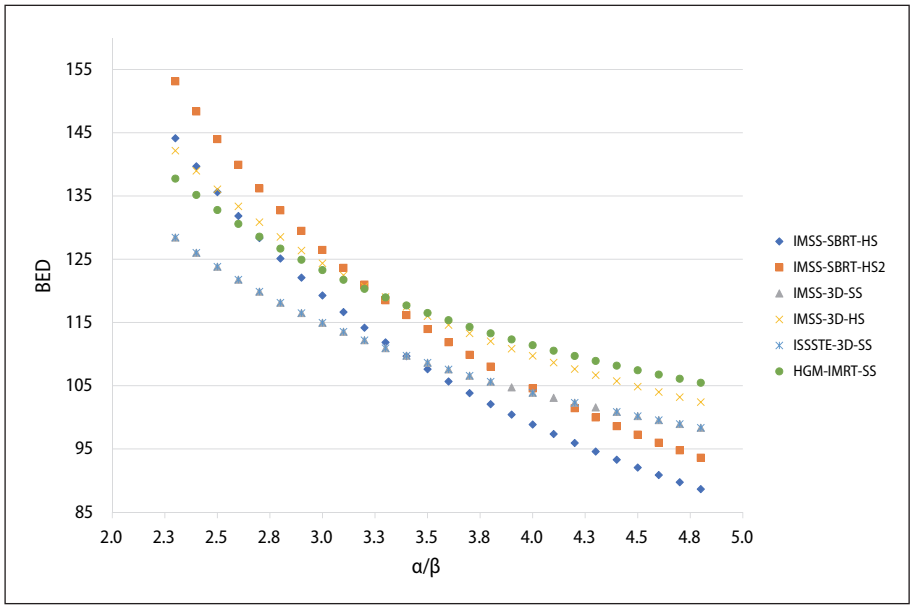

Figure 1. Biologically effective dose (BED) *vs.* α/β ratio for three cohorts of Mexican prostate cancer (PCa) patients treated with three external radiotherapy techniques: stereotactic body radiation therapy (SBRT), three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) at three public Mexican institutions: IMSS, ISSSTE and HG. SS — standard scheme; HS — hypofractionated scheme

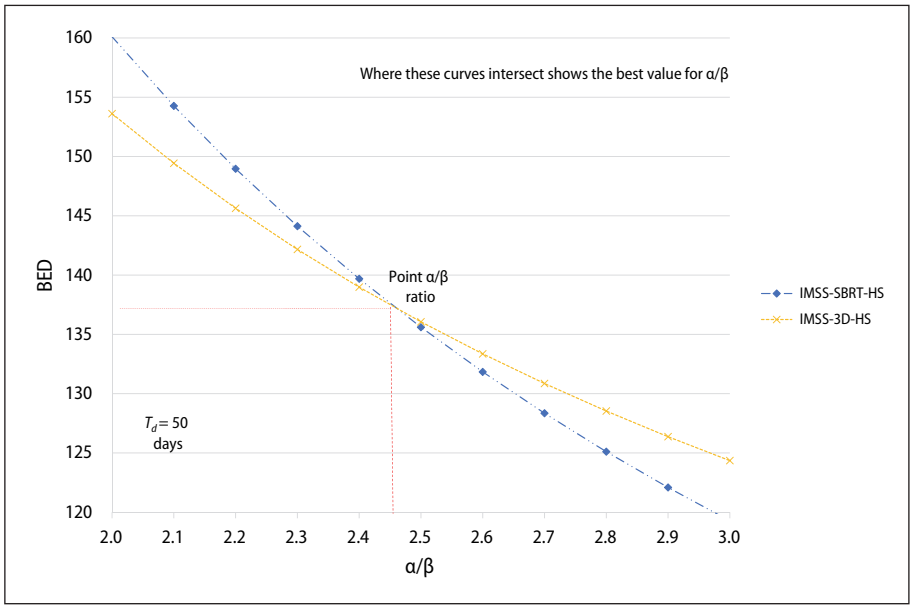

Figure 2. α/β = 2.46 Gy, associated with the IMSS-SBRT-HS *vs.* IMSS-3D-HS treatment arms

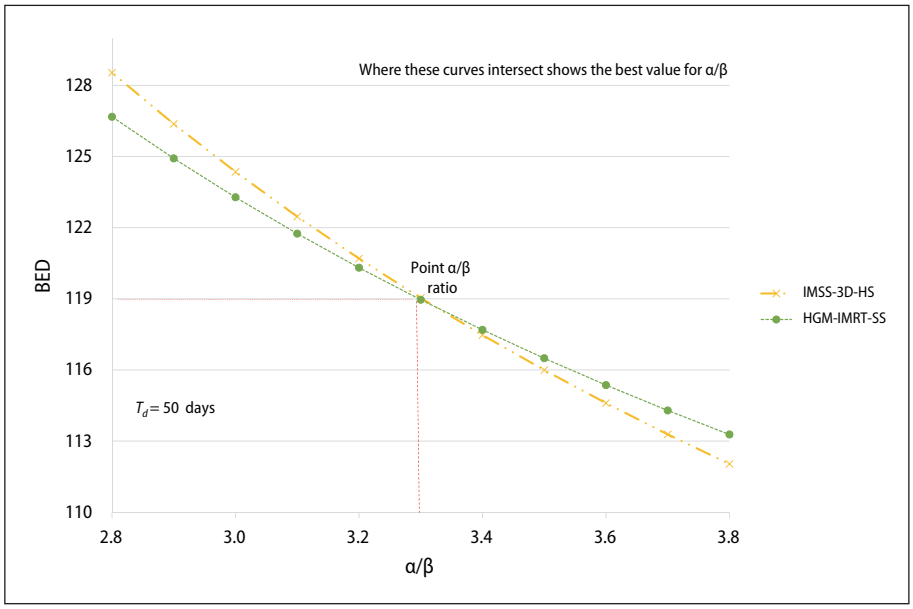

Figure 3. IMSS-3D-HS *vs.* HGM-IMRT-SS treatment schemes, α/β = 3.30 Gy

to the pair of treatment schemes IMSS-3D-HS *vs* HGM-IMRT-SS;

- next, the Figure 4 shows the pair of treatments arms IMSS-SBRT-HS2 *vs.* HGM-IMRT-SS, where there is a third point for α/β 3.25 Gy;
- in addition to the above, a fourth and a fifth value of α/β is found at the intersection of 3.24 Gy for the IMSS-SBRT-HS *vs* ISSSTE-3D-SS and 3.38 Gy for the IMSS-3D-HS *vs* IMSS-SBRT-HS2 schedules respectively (Fig. 5).
- finally, an α/β is present in Figure 6, with a value slightly higher than the rest (4.08 Gy), for the IMSS-SBRT-HS2 *vs* ISSSTE-3D-SS treatment arms.

The different values of α/β can be explained as follows: a) the bRFS's do meet the H_0 of being equal, but have a statistical variability associated with the significance level alpha, b) the absorbed dose D delivered to the patient presents an expanded uncertainty that has not been considered [5], c) the

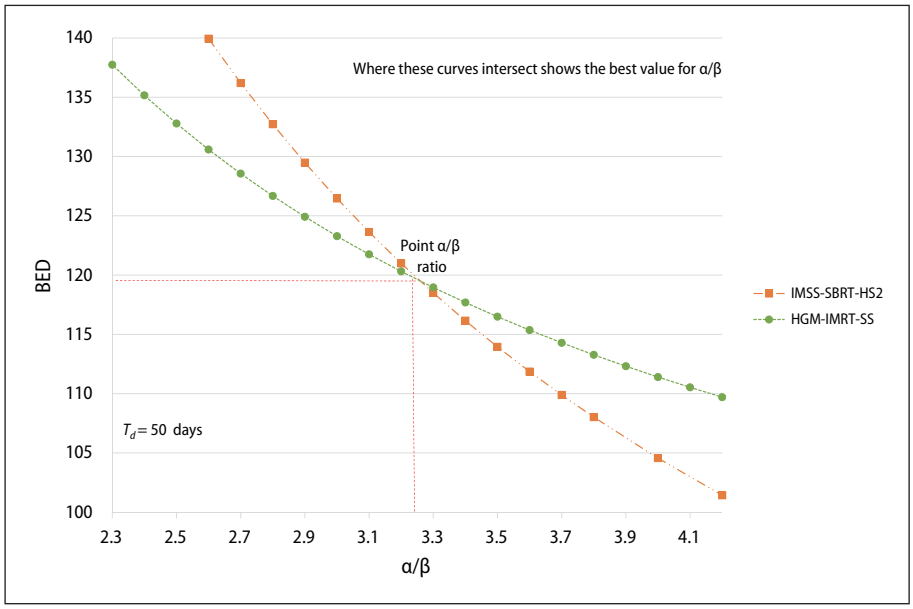

Figure 4. Intersection point for IMSS-SBRT-HS2 *vs.* HGM-IMRT-SS, α/β = 3.25 Gy

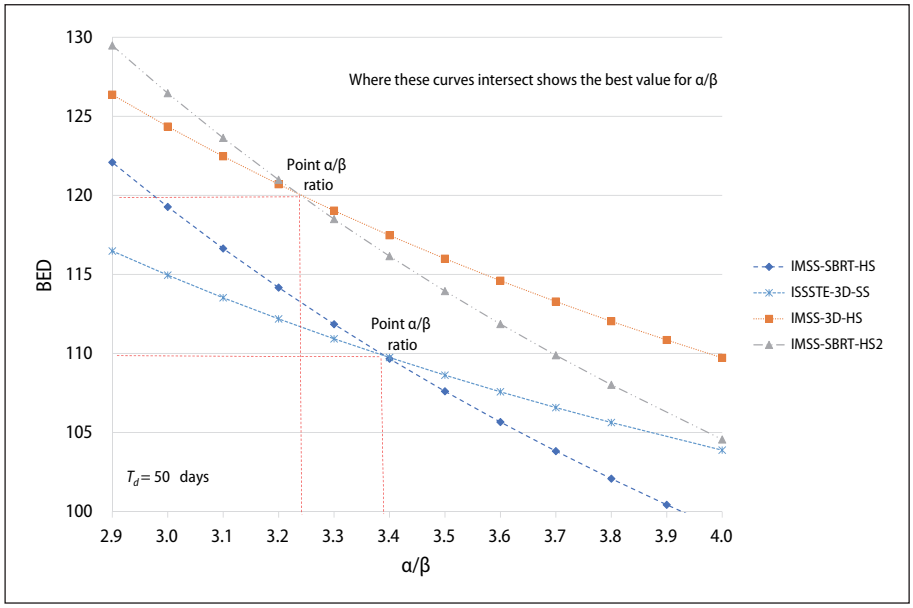

Figure 5. α/β's for the IMSS-SBRT-HS *vs.* ISSSTE-3D-SS and IMSS-3D-HS *vs.* IMSS-SBRT-HS2 treatment schemes, respectively

$\underline{\alpha/\beta}$ for all the schemes have an average value of $\alpha/\beta = 3.29\ (\pm\ 0.52)$ Gy, d) this interval value is compatible and consistent with the results determined by using the time-dependent LQ models in previous publications [6, 7, 15].

However, in Eq. (2) additional factors are taken into account [20]: N, T, T_k and T_d; which are presented as a function of the risk group. In fact, the section: Biologically Effective Dose Model in [20] explains the importance of the temporal parameters; where they are manifested as a loss of tumor control through repopulation, which manifests itself as an underestimation of the α/β ratio [1, 6].To emphasize this, remember that the medical physicist employs these parameters in the clinical practice to solve the problems of the *gap treatment.*

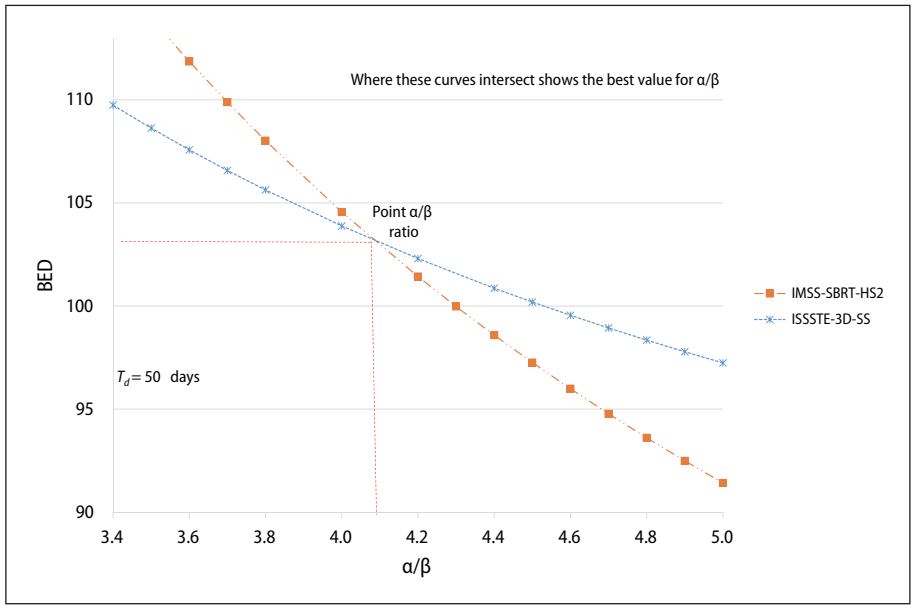

Figure 6. α/β = 4.08 Gy for the IMSS-SBRT-HS2 *vs.* ISSSTE-3D-SS for both schedules

Discussion

It is important to note that for each fractionation scheme, the BED and EQ_2 on Table 1 are calculated using clinical protocols that assume a relationship of 1.4 Gy [1]. But the calculation of the BED and EQ_2 in Table 2 is prepared with the $\overline{\alpha/\beta}$ = 3.29 Gy determined for the cohort of Mexican PCa patients.

Analyzing the values of EQ_2 obtained with the $\overline{\alpha/\beta}$ = 3.29 Gy, it is observed that these values decreased by up to 20% for the hypofractioned schemes with respect to those shown in Table 1. Specifically, this verifies that the value $\overline{\alpha/\beta}$ = 3.29 Gy is logically consistent with the EQ_2 values. In fact, since the new values for EQ_2's calculated consider the temporal dependence are in order of 72–76 Gy, it means that these values are coherent with those of conventional treatment schemes. Therefore, from the point of view of radiobiological optimization, the $\overline{\alpha/\beta}$ = 3.29 (± 0.52) Gy is what best fits the survival curves of the Mexican population for the treatment of PCa.

It seems that there is a great variation in the extremes of the α/β ratio for the schemes studied in this work, but different studies have found similar ratios [6, 15, 20]. However, as mentioned previously, the temporal dependence of the LQ model should not be omitted since it implies the risk of making biased estimates of the α/β ratio.

Another important point is to consider the effect of uncertainty in the total dose administered to the patient and its influence on the bRFS response,

Table 2. Biologically effective doses (BED) and equivalent doses (EQ2) of the different treatments using α/β = 1.4 Gy and $\overline{\alpha/\beta}$ = 3.29 Gy determined for a Mexican cohort of prostate cancer (PCa) population

Technique	Dose fx [Gy]	Fractions [n]	EQ_2 [Gy] α/β Gy k = 0.1 Gy/day	BED [Gy] α/β Gy k = 0.1 Gy/day	EQ_2 [Gy] α/β Gy k = 0.1 Gy/day	BED [Gy] α/β Gy k = 0.1 Gy/day
3D-CRT	1.8	39–44	62–70	157–177	64–72	105–118
3D-CRT	2.66	25	77	190	73	118
SBRT	7	5	90	214	72	113
SBRT	7.25	5	92	228	76	120
3D-CRT	1.8–2.0	30–41	58–66	143–165	58–67	94–110
IMRT	1.8	42–44	67–70	169–177	69–72	113–118

3D-CRT — three-dimensional conformal radiation therapy; SBRT — stereotactic body radiation therapy; IMRT — intensity-modulated radiation therapy

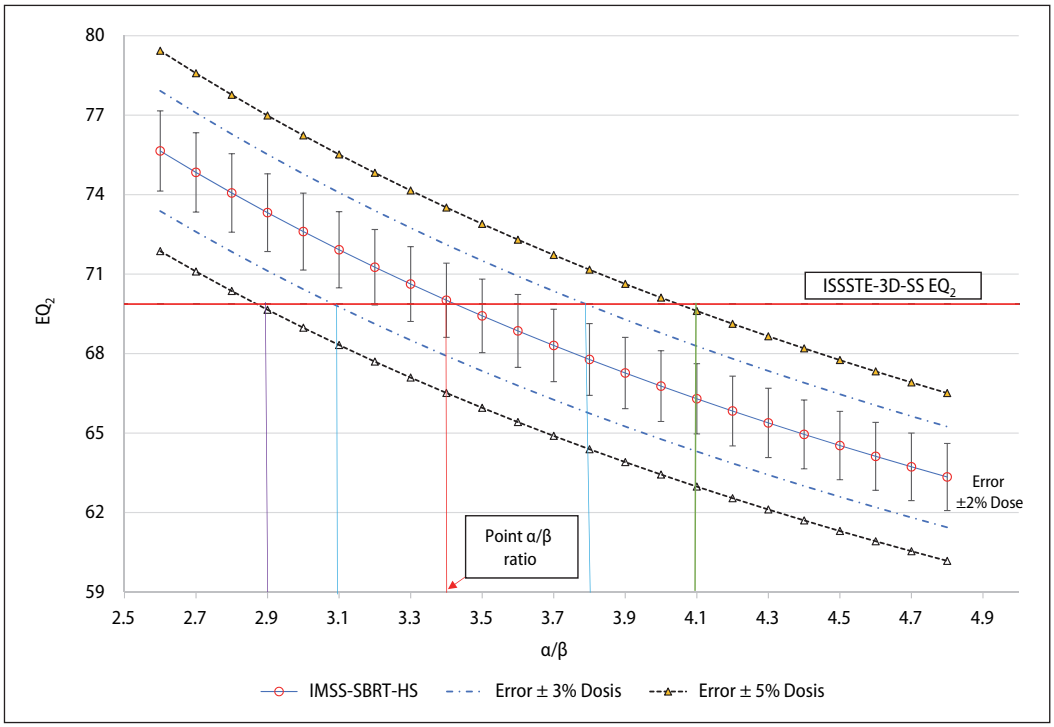

Figure 7. Uncertainties introduced for equvalent dose (EQ2) *vs.* the α/β ratio for the IMSS-SBRT-HS scheme. EQ2 with different u_c ± 2%, ± 3% and ± 5% are calculated to generate the curves

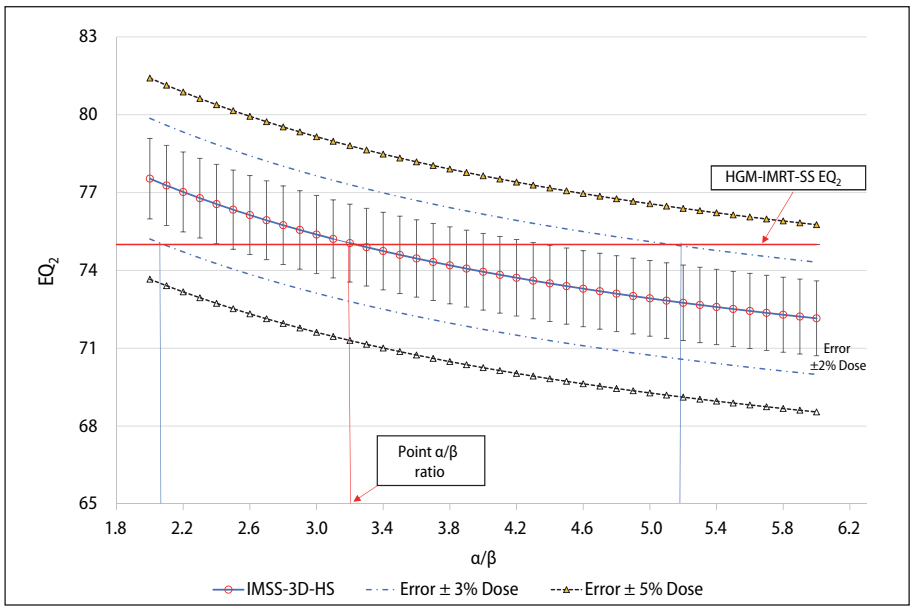

Figure 8. u_c introduced for equivalent dose (EQ2) *vs.* the α/β ratio for IMSS-3D-HS scheme. Doses different by ±2%, ±3% and ±5% are calculated to generate the curves

which has not been addressed in detail in the modern literature for these type of treatments for PCa [20]. To demonstrate this with a simple exercise, Figures 7 and 8 were performed to exemplify what could happen for the α/β values if there was an uncertainty in the absorbed dose administered to the patients. For such an example, ± 2% combined uncertainty (u_c) bars and curves with an u_c of ± 3% and ± 5% in the absorbed dose, respectively, are introduced.

In the Figure 7 it is shown with an u_c in the total absorbed dose administered to the patient of ± 5%, it could cause a great variation in the radiobiological parameter α/β changing its value for this example from 2.9 Gy to 4.1 Gy, respectively. On the other hand, if you had a deviation of ±3% in the total absorbed dose, you would have an approximate α/β of 3.1 Gy to 3.8 Gy, respectively.

In the same way, in Figure 8 errors were induced in the total absorbed dose and concentrating on the corresponding u_c = ± 3%, we can see that the alpha/beta ratio increases from 2.1 to 5.2 Gy.

Figures 7 and 8 are simply an illustration of the wide variation that can occur in the results due to possible random u_c [5].

Conclusions

This study confirms that the main disadvantage of the treatment of PCa with standard schemes of radiotherapy is the duration of the treatment. This means that the possibility of reducing the treatment time, delivering higher absorbed doses per fraction, has benefits from an economic and administrative point of view. Improving and optimizing the use of technical and human resources allows the patient to finish his treatment in a shorter period. The cost of treatment is lower for the institution and the patient. This will increase access to treatment for more patients.

From Figures 1–6 it is concluded that the average value for $\overline{\alpha/\beta}$ = 3.29 (± 0.52) Gy for a cohort of Mexican patients with PCa treated with external radiotherapy.

Using the time-dependent LQ model it is observed that the value $\overline{\alpha/\beta}$ = 3.29 (± 0.52) is higher than 1.5 Gy calculated with basic LQ models (without temporal dependence); where our interval value α/β is compatible and consistent with the results determined with the time-dependent LQ models on previous publications [6, 7]. It is worth mentioning that our α/β is calculated considering k = 0.1 Gy/day, with T_d = 50 days, T_k = 30 days and $\overline{\alpha}$ = 0.130 (± 0.010) Gy.

The most important conclusion is that once the relationship optimized $\overline{\alpha/\beta}$ ratio of 3.29 Gy was validated for the Mexican population, it could be used as an accurate and precise radiobiological parameter for the design of external RT fractionation schemes to optimize treatment of PCa in the Mexican population and improve their bRFS values.

Finally, it is necessary to continue with an exhaustive study of the LQ model as a function of time with the data of the Mexican patients with PCa.

Conflicts of interest

The authors have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers 'bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Funding

None declared.

Acknowledgements

We thank the Education Department of all Medical Centers for the facilities given in obtaining data of the treated patients, where all data is protected by confidentiality regulations. MSc. Adame appreciates the support given by RMyT to carry out this research work; Dr. Alvarez wishes to thank the SSDL/ININ for allowing time for the development of this work; we are also very grateful that the ESFM/IPN allowed Dr. Moranchel to carry out this research.

References

1. Cosset JM, Chargari C, Créhange G. [Which alpha/beta ratio for prostate cancer in 2019?]. Cancer Radiother. 2019; 23(4): 342–345, doi: 10.1016/j.canrad.2019.01.004, indexed in Pubmed: 31122867.
2. Cancer Today. https://gco.iarc.fr/today/online-analysis-multi-bars?v=2018&mode=cancer&mode_population=countries&population=900&populations=484_388&key=total&sex=1&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_ite (July 24, 2020).
3. Howlader N, Krapcho M, Miller D et al. Cancer Statistics Rev 1975–2014 — SEER Statistics. SEER Cancer Statistics Review — Bethesda (MD): National Cancer Institute. . https://seer.cancer.gov/archive/csr/1975_2014/ (July 25, 2020).
4. Haiman CA, Chen GK, Blot WJ, et al. Characterizing genetic risk at known prostate cancer susceptibility loci in African Americans. PLoS Genet. 2011; 7(5): e1001387, doi: 10.1371/journal.pgen.1001387, indexed in Pubmed: 21637779.

5. Dekkers G. Accuracy Requirements and Uncertainties in Radiotherapy. IAEA Human Health Series. 2016; 31, doi: 10.1111/insr.12068_10.
6. Vogelius IR, Bentzen SM. Dose Response and Fractionation Sensitivity of Prostate Cancer After External Beam Radiation Therapy: A Meta-analysis of Randomized Trials. Int J Radiat Oncol Biol Phys. 2018; 100(4): 858–865, doi: 10.1016/j.ijrobp.2017.12.011, indexed in Pubmed: 29485063.
7. Datta NR, Stutz E, Rogers S, et al. Clinical estimation of α/β values for prostate cancer from isoeffective phase III randomized trials with moderately hypofractionated radiotherapy. Acta Oncol. 2018; 57(7): 883–894, doi: 10.1080/0284186X.2018.1433874, indexed in Pubmed: 29405785.
8. Tree AC, Dearnaley DP. Seven or less Fractions is Not the Standard of Care for Intermediate-Risk Prostate Cancer. Clin Oncol (R Coll Radiol). 2020; 32(3): 175–180, doi: 10.1016/j.clon.2019.10.006, indexed in Pubmed: 31711737.
9. Arribalzaga E. Interpretación de las curvas de supervivencia. Revista chilena de cirugía. 2007; 59(1), doi: 10.4067/s0718-40262007000100013.
10. Mayles P, Nahum A, Rosenwald JC. Handbook of Radiotherapy Physics: Theory and Practice. Taylor & Francis, New York 2007.
11. Miralbell R, Roberts SA, Zubizarreta E, et al. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β = 1.4 (0.9-2.2) Gy. Int J Radiat Oncol Biol Phys. 2012; 82(1): e17–e24, doi: 10.1016/j.ijrobp.2010.10.075, indexed in Pubmed: 21324610.
12. Fowler J, Chappell R, Ritter M, et al. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys. 2001; 50(4): 1021–1031, doi: 10.1016/s0360-3016(01)01607-8, indexed in Pubmed: 11429230.
13. Leborgne F, Fowler J. Late outcomes following hypofractionated conformal radiotherapy vs. standard fractionation for localized prostate cancer: a nonrandomized contemporary comparison. Int J Radiat Oncol Biol Phys. 2009; 74(5): 1441–1446, doi: 10.1016/j.ijrobp.2008.10.087, indexed in Pubmed: 19395194.
14. Leborgne F, Fowler J, Leborgne JH, et al. Later outcomes and alpha/beta estimate from hypofractionated conformal three-dimensional radiotherapy versus standard fractionation for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2012; 82(3): 1200–1207, doi: 10.1016/j.ijrobp.2010.12.040, indexed in Pubmed: 21477933.
15. van Leeuwen CM, Oei AL, Crezee J, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol. 2018; 13(1): 96, doi: 10.1186/s13014-018-1040-z, indexed in Pubmed: 29769103.
16. Ferreira MR, Thomas K, Truelove L, et al. Dosimetry and Gastrointestinal Toxicity Relationships in a Phase II Trial of Pelvic Lymph Node Radiotherapy in Advanced Localised Prostate Cancer. Clin Oncol (R Coll Radiol). 2019; 31(6): 374–384, doi: 10.1016/j.clon.2019.02.012, indexed in Pubmed: 30902559.
17. Decree by which various provisions of the Mexican General Health Law are amended and added. Registry. Official Journal of the Federation DOF 17/07/2018. Accessed July 26, 2020. Mexico City, Mexico. (in Spanish).
18. Regulation of the National Cancer Registry. Official Journal of the Federation DOF: 17/07/2018. Published online 2021:1-2. Mexico City, Mexico. (in Spanish).
19. Adame González C, Álvarez Romero JT, Morachel Y Rodríguez M, et al. Biochemical relapse free survival rate in patients with prostate cancer treated with external radiotherapy: outcomes obtained at the CMN Siglo XXI Hospital de Oncología, CMN 20 de Noviembre and Hospital General de México of the México City. Rep Pract Oncol Radiother. 2020; 25(2): 276–281, doi: 10.1016/j.rpor.2020.02.003, indexed in Pubmed: 32140086.
20. Pedicini P, Strigari L, Benassi M. Estimation of a self-consistent set of radiobiological parameters from hypofractionated versus standard radiation therapy of prostate cancer. Int J Radiat Oncol Biol Phys. 2013; 85(5): e231–e237, doi: 10.1016/j.ijrobp.2012.11.033, indexed in Pubmed: 23332226.
21. Donald Chapman J, Nahum AE. Radiotherapy Treatment Planning: Linear-Quadratic Radiobiology. Taylor & Francis, New York 2015.
22. Fowler J. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989; 62(740): 679–694, doi: 10.1259/0007-1285-62-740-679, indexed in Pubmed: 2670032.
23. Khan FM, Gibbons JP, Sperduto PW. Treatment Planing in Radiation Oncology. 4th ed. Wolters Kluwer 2016.