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FULL PAPER

Prostate cancer dose-response, fractionation sensitivity and repopulation parameters evaluation from 25 international radiotherapy outcome data sets

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Objective: This study was undertaken to model the biochemical free survival at 5 years and to evaluate the parameters defining dose-response curve, dose-fractionation radiosensitivity and repopulation.

Methods: It was carried out a literature search on Pubmed to retrieve data sets of patients treated with external beam radiation therapy of 1.8–4.0 Gy per fraction and overall treatment time of 3 to 10 weeks. 10 groups were identified, based on risk class and androgen deprivation therapy (ADT). Dose-response curve D_{50} (dose at 50% probability of control) and g_{50} (steepness), α/β (dose-fractionation radiosensitivity), and repopulation parameters, d_{prolif} and T_{prolif} , were calculated. Bootstrap-based cross-validation was performed and median and 95% CI (confidence interval) were evaluated.

Results: 25 data sets, including 20,310 patients, were considered. The median (95% CI) D_{50} and g_{50} values were 62 (CI 53 – 66) Gy and 1.6 (0.8 – 2.4). ADT patients

showed lower values of D_{50} and g_{50} (57 ± 5 Gy and 1.1 ± 0.4) compared to no-ADT patients (65 ± 2 Gy and 2.3 ± 0.6), with $p < 0.0001$ and $p = 0.002$. If we did not consider any dependence on overall treatment time, the median (95% CI) value of α/β was 1.4 (1.0 – 1.9) Gy with $p < 0.0001$ for all patients. The median values of d_{prolif} and T_{prolif} were 0.0 to 0.3 Gy/d and 18–40 days.

Conclusion: Dose-response curve resulted dependent on risk class and ADT, with higher steepness for no-ADT patients. Low values of dose-fractionation radiosensitivity were found, supporting the use of moderate hypofractionated radiotherapy in each risk class. A limited dependence on repopulation was observed.

Advances in knowledge: Prostate cancer response to moderate hypofractionated radiotherapy was reliably quantified considering risk class and androgen deprivation therapy.

INTRODUCTION

The value and variability of radiosensitivity and overall treatment time (OTT) parameters that influence the effectiveness of radiation therapy in prostate cancer are still debated.^{1–22}

A recurring question concerns the response of the system to changes in dose per fraction (α/β): “is the α/β ratio for prostate cancer low?”^{3,5,9} A low α/β ratio indicates a high sensitivity to fractionation similar to late-responding normal tissue.^{2,6,7} This question is equivalent to asking whether the α/β value for prostate cancer is atypically lower than those usually ascribed to acute effects and most other types of tumor.^{1,4,5,15}

A second question, connected to the previous one, but different and more stringent: “is the α/β value for prostate cancer lower than the α/β values of the surrounding late responding tissues at risk?”^{7,10} or even, from a more important clinical point of view: “do hypofractionated protocols create a clinical gain for the prostate?”^{9,14,15,17–19} Rectum and bladder, being adjacent to the prostate, are primarily at risk, presenting important late toxicities that follow some dose-volume response curves.^{7,14,15,23–25} Therefore, if the α/β value for prostate cancer would be really lower than those of rectum and bladder for late-responding sequelae, hypofractionated schedules could be implemented with fewer fractions but larger dose per fraction, to maintain equivalent late effects while yielding a better tumor control.^{7,11,14,15,21}

A third question, less analyzed so far: “is the effect of tumor repopulation negligible in determining the local tumor control in radiotherapy treatments?”^{1,2,6–8,13,14,16,18,20,22} It was reported that the effect of tumor repopulation is not negligible for the accurate description of the prostate radiation therapy, especially for the brachytherapy permanent implants.⁸ Other authors reported that prostate cancer patients had a statistically significant detriment with a prolonged external beam radiation therapy (EBRT) treatment duration, encouraging to avoid more than four treatment breaks in a course of 40 fractions.¹³ Similarly, another study concluded that an improvement in outcomes may be obtained by modest decreases in OTT.¹⁶

The impact of ADT on the radiosensitivity and patient survival is discussed in literature. Few studies reported that α/β value is not affected by the use of ADT,^{18,19} whereas the relevance of ADT on the tumor control probability (TCP) is generally accepted for intermediate and high risk patients,^{26–28} although the duration and the clinical protocol used may influence the outcome.^{29–31}

Even though it has been proved that the practice of dose escalation, allowed by the implementation of radiotherapy techniques,^{32–34} improves the TCP, it still remains unclear if there are different fractionation sensitivities for different risk groups or if increase in TCP depends on the concurrent use of ADT.

Furthermore, it must be noted that different TCP indicators are used at 5, 10 or more years,^{29,35} and that the 5y biochemicalfree survival (BCFS) finds a large dispersion and should be considered a short-term TCP indicator for prostate cancer.^{36–38}

Therefore, the aim of this work is to model the 5y BCFS short term dose–response using the clinical data reported in literature on patients treated with EBRT, with or without ADT association. Moreover, the sensitivity of TCP to fraction size (α/β) and repopulation parameters is evaluated, stratified for patient risk classes and use of ADT.

METHODS AND MATERIALS

Literature search strategy and selection criteria

The studies were searched through PubMed using the string “prostate” AND “radiotherapy” AND “dose-response” (Figure 1). This search included publication dates up to June 30, 2018. Data sets were identified based on inclusion criteria: 5y BCFS reported according to the Phoenix criterion³⁹ and dosimetric, ADT-related and clinical information described, radical treatment (no post-operative and palliative radiotherapy), photon EBRT alone (no proton and brachytherapy boost), moderate hypofractionation with dose per fraction and OTT between 1.8–4.0 Gy/fr and 3–10 weeks (no stereotactic ablative radiotherapy) and one fraction per day (no twice-daily fractions) remaining constant during all the course.

Data sets from randomized trials and retrospective studies were considered from more recent original papers^{11,34,40–60}; three of them were selected from two reviews.^{19,22} No assessment of the risk of publication bias was conducted. The investigators of the original studies were not contacted to have further data. All

relevant information extracted from the studies and describing the selected data sets was synthesized in Table 1 and in Tables Is and IIs in Supplementary Material 1.

Patients stratification

According to the National Comprehensive Cancer Network guidelines risk group classification⁵⁹ and the use of ADT, patients of clinical data set of Table 1 were stratified into 10 groups (Table 2). Substratification of ADT (duration, neoadjuvant vs concomitant vs adjuvant) was not investigated. Each sub data set considered in Tables Is and IIs included at least 40 patients at the beginning of the follow-up.

Statistical analysis

The dose–response curves were designed using the standard dose scheduling (*i.e.* exclusively considering treatments of 2 Gy/fraction and 5 fractions per week) (Table Is) and applying the two parameters—the logistic model²⁰:

$$p_{5yBCFS}(D) = \frac{1}{1 + \exp(4g_{50}(1 - D/D_{50}))} \quad (1)$$

where: p_{5yBCFS} is the 5 years BCFS associated to the total dose D delivered with standard dose scheduling, *i.e.* the equivalent dose in 2 Gy per fraction (EQD2). D_{50} and g_{50} are the parameters of the model: D_{50} is the value of dose at 50% value of p_{5yBCFS} , while g_{50} is the multiplicative factor of the percent dose variation at D_{50} used to find the absolute variation of $p_{5yBCFS}(D_{50})$.⁶¹

Non-linear constrained least square regression was applied using R statistical software⁶² with the lower and upper bounds of the constraints set within the range of 25 Gy $< D_{50} < 100$ Gy and 0.15 $< g_{50} < 10$. The R software was used to estimate the coherence of model fit, evaluating standard error of estimation (SEE), standardized residuals, normal Q–Q representation, covariance matrices and generalized ellipsoids of 95% confidence interval (CI).⁶³ Two-sample *t*-test with unequal variances was used to compare averages. A bootstrap-based cross-validation was performed and average, standard deviation, median and 95% CI percentiles-based of fit parameters were calculated.^{62,63}

For each no standard dose schedule of Table IIs, the total dose in the 2 Gy equivalent scheduling that should produce the iso-effective tumor outcome (D_{equi}) was calculated, as described in appendix A of SM, using the bootstrap median values of the parameters.

The radiosensitivity to the dose fractionation (α/β) and the parameters expressing the tumor-cells repopulation,^{16,18,19} the dose lost per day (d_{prolif}) and the time delay before the onset of proliferation (T_{prolif}), were determined for each group under three different hypotheses: EQD2 independence or dependence on OTT and EQD2 dependence on OTTs difference. A non-linear constrained least square regression⁶⁴ was applied to find parameters values, minimizing the expression, E , given by:

$$E = \sum_i^M (D_{equi}^i - D_2^i)^2 \quad (2)$$

Figure 1. Literature search strategy and selection of clinical data sets. ADT, androgen deprivation therapy; 5y BCFS, biochemical free survival at five years; SABR, stereotactic ablative radiotherapy.

where D_2^i is the EQD2 of i -th no standard dose scheduling of Table II for a patients group of Table 2. D_2^i is a function of α/β , d_{prolif} and T_{prolif} implicitly defined, by equating the biological effective dose⁶⁵ as described in Appendix B.

Also, a bootstrap-based cross-validation of fit parameters α/β , d_{prolif} and T_{prolif} was performed.^{62,63} A home-made R script to perform and check non-linear minimization was developed (appendix C of SM).

RESULTS

25 clinical data sets, including 20,310 patients, describing the 5y BCFS and reporting dosimetric, ADT-related and clinical information, were considered in Table 1. The collected data sets included 14 randomized clinical trials, 2 prospective trials and 9 retrospective studies.

The results of non-linear constrained least square regression of the logistic model, parameter values with their standard error and p -values, SEE, median and 95% CI of the bootstrap-based

cross-validated parameters were reported in Table III of Supplementary Material 1. The average relative SEE value was about 10%. Regression p -values <0.003 and <0.05 for D_{50} and g_{50} were obtained for all groups. The values of D_{50} and g_{50} from the bootstrap-based cross-validated fit of the dose-response curve were reported in Figure 2.

Considering the group “All” (all patients), the least square regression estimations of D_{50} and g_{50} were 62 ± 2 Gy ($p < 0.0001$) and 1.6 ± 0.3 ($p < 0.0001$) while the bootstrap median (95% CI) values were 62 (53–66) Gy and 1.6 (0.8–2.4). The median of D_{50} and g_{50} values for low (“L”), intermediate (“I”) and high risk (“H”) patients were 54 Gy and 1.4, 62 Gy and 2.0 and 69 Gy and 2.0.

In Figure 3, the plots of bootstrap-based cross-validated dose-response curve with standard dose scheduling for the patients of groups “L” (low risk), “I” (intermediate risk) and “H” (high risk) with 95% CI were shown, visually highlighting the frank dependence on the risk class even considering the bootstrap-based confidence intervals.

Table 1. Summary of clinical data sets

Reference	Trial	Trial type	Recruiting period	Patients	Risk class	Pelvic node RT	Dose scheduling	Treatment technique	ADT
Lukka 2005 ¹¹	Canadian hypo	Randomised, Phase 3, multicenter	1995–1998	936	L//H	No	66 Gy at 2 Gy/fr and 52.4 Gy at 2.62 Gy/fr	Pre-/3D-CRT	No
Miralbell 2012 ¹⁹	England–Logue	-	-	2082	L//H	No	50 Gy at 3.125 Gy/fr	3D-CRT	No/NHT/AHT
Miralbell 2012 ¹⁹	Uruguay–Leborgne	-	-	867	L//H	No	76 Gy at 2 Gy/fr	3D-CRT	No/NHT/AHT
Pedicini 2013 ²²	MSKC DE	-	-	210	I	No	68.4 Gy and 79.2 Gy at 1.8 Gy/fr	-	No/NHT
Kupelian 2005 ^{40†}	Cleveland 78 Gy	Retrospective, single-institution	1993–2005	561	L//H	No	78 Gy at 2 Gy/fr	3D-CRT	No/NHT/AHT
Higgins 2006 ⁴¹	ECC hypo	Retrospective, single-institution	1996–2001	300	L//H	No	52.5 Gy at 2.625 Gy/fr	Pre-/3D-CRT	NHT
Dearnaley 2007 ⁴²	MRC_RT01	Randomized, Phase 3, multicenter	1998–2001	843	L//H	No	64 Gy and 74 Gy at 2 Gy/fr	3D-CRT	NHT
Kupelian 2007 ⁴³	Cleveland hypo	Retrospective, single-institution	1998–2005	770	L//H	No	70 Gy at 2.5 Gy/fr	IMRT	No/NHT/AHT
Lawton 2007 ^{44§}	RTOG_94_13_II_IV	Randomized, Phase 3, multicenter	1995–1999	640	H	No	70.2 Gy at 1.8 Gy/fr	3D-CRT	NHT/AHT
Kuban 2008 ⁴⁵	MDAnderson DE	Randomized, Phase 3, single-institution	1993–1998	301	L//H	No	70 Gy and 78 Gy at 2 Gy/fr	Pre-/3D-CRT	No
Beckendorf 2011 ³⁴	GETUG_06_1	Randomized, Phase 3, multicenter	1999–2000	306	L//H	No	70 and 80 Gy at 2 Gy/fr	3D-CRT	No
Yeoh 2011 ⁶⁰	RAH hypo	Randomized, Phase 3, single-institution	1996–2003	217	L//H	No	64 Gy at 2 Gy/fr and 55 Gy at 2.75 Gy/fr	Pre-/3D-CRT	No
Valicenti 2011 ⁴⁶	RTOG_94_06	Randomized, Phase 1/2, multicenter	1994–2000	883	L//H	No	79.2 Gy at 1.8 Gy/fr	3D-CRT	No/NHT/AHT
Alickus 2011 ⁴⁷	MSKC IMRT	Retrospective, Phase 1, single-institution	1996–1998	170	L//H	No	81 Gy at 1.8 Gy/fr	IMRT	No/NHT
Fonteyne 2012 ⁴⁸	IRE_GUH_UZB hypo	Prospective, Phase 2, multicenter	2004–2006	113	L//H	No	56 Gy at 3.5 Gy/fr with four fr/w	IMRT	No/NHT/AHT
Spratt 2012 ⁴⁹	MSKC DEH	Prospective, Phase 1, single-institution	1997–2008	1002	L//H	No	86.4 Gy at 1.8 Gy/fr	IMRT	No/NHT/AHT
Pollack 2013 ⁵⁰	FCCC hypo	Randomized, Phase 3, single-institution	2002–2006	303	L//H	No/Yes	76 Gy at 2 Gy/fr and 70.2 Gy at 2.7 Gy/fr	IMRT	No/NHT/AHT
Heemsbergen 2014 ⁵¹	Dutch NCT00692107	Randomized, Phase 3, multicenter	1997–2003	664	L//H	No	68 Gy and 78 Gy at 2 Gy/fr	3D-CRT/IMRT	No/NHT/AHT
Gabriele 2016 ⁵²	Eureka-2	Retrospective, multicenter	1997–2012	2493	L//H	No/Yes	Multi-fractionation schedules	3D-CRT/IMRT	No/NHT/AHT

(Continued)

Table 1 (Continued)

Reference	Trial	Trial type	Recruiting period	Patients	Risk class	Pelvic node RT	Dose scheduling	Treatment technique	ADT
Dearnaley 2016 ⁵³	CHHiP	Randomized, Phase 3, multicenter	2002–2011	3216	L/I/H	No	74 Gy at 2 Gy/fr and 57 Gy and 60 Gy at 3 Gy/fr	IMRT	No/NHT
Kountoury 2016 ⁵⁴	GVA – BCN hypo	Retrospective, two-institution	2003–2010	163	L/I/H	No	56 Gy and 60 Gy with two fr/w at 4. Gy/fr	IMRT	No/NHT/AHT
Lee 2016 ⁵⁵	RTOG_04_15	Randomized, Phase 3, multicenter	2006–2009	1092	L	No	73.8 Gy at 1.8 Gy/fr and 70 Gy at 2.5 Gy/fr	3D-CRT/IMRT	No
Incrocci 2016 ⁵⁶	HYPRO	Randomized, Phase 3, multicenter	2007–2010	804	I/H	No	78 Gy at 2 Gy/fr and 64.6 Gy at 3.4 Gy/fr	3D-CRT/IMRT	No/NHT/AHT
Arcangeli 2017 ⁵⁷	IRE hypo	Randomized, Phase 3, single-institution	2003–2007	168	H	No	80 Gy at 2 Gy/fr and 62 Gy with four fr/w at 3.1 Gy/fr	3D-CRT	NHT/AHT
Catton 2017 ⁵⁸	PROFIT	Randomized, Phase 3, multicenter	2006–2011	1206	I	No	78 Gy at 2 Gy/fr and 60 Gy at 3 Gy/fr	3D-CRT/IMRT	No

ADT, androgen deprivation therapy; AHT, adjuvant hormonal therapy; 3D-CRT, three-dimensional conformal radiotherapy; H, high risk; I, intermediate risk; IMRT, intensity-modulated radiation therapy; L, low risk; NHT = neoadjuvant hormonal therapy; RT, radiotherapy.
 Note: #in Miralbell et al(19), the number of patients is 561; in Kupelian et al (40), it was 310. \$The number of patients of the four arms of the trial was 1323. For each trial, detailed values of 5y BCFS (biochemical free survival at 5 year), number of fractions, total dose and OTT (overall treatment time) are provided in the Supporting Information in the tables I and IIs.

Assuming no dependence on OTT, the α/β values, were reported in Figure 4 and in Table IVs of SM. For each group, the value of SEE was always less than 7.6 Gy (about 10%). For each group, the regression estimations and bootstrap median values of α/β were included between 0.9 and 1.9 Gy, with $p < 0.02$ and standard deviation < 0.5 Gy. Median (95% CI) α/β values of 1.4 (1.0–1.9) Gy, 1.3 (0.8–2.2) Gy, 1.9 (1.3–2.7) Gy, 1.3 (0.7–1.3) Gy and 1.5 (1.0–2.2) Gy were obtained for all (“All”), low (“L”), intermediate (“I”), high (“H”) and intermediate-high (“IH”) groups.

In Figure 3, plots of 5y BCFS against EQD2 and, in Figure 5, plots of 5y BCFS obtained from EQD2 against experimental 5y BCFS for patients with no standard dose scheduling of groups “L”, “I” and “H” were reported. From plots of Figure 5, bias and uncertainty on 5y BCFS, due to the use of median value of α/β and without considering any dependence on OTT, can be easily evaluated.

The α/β , d_{prolif} and T_{prolif} values were reported in Table Vs of SM assuming OTT dependence, while α/β and d_{prolif} values were shown in Table VIs of SM assuming the dependence on the OTTs differences, that is with no lag time before accelerated repopulation. An increase in the α/β value and also in the width of the bootstrap 95% CI was observed. The fit values and bootstrap median values of d_{prolif} were always included in the range of 0.0–0.3 Gy/d and of 0.0–0.2 Gy/d assuming no lag time. The difference between bootstrap median values of d_{prolif} , considering or not the lag time (Table Vs vs Table VIs), was lower than 0.1 Gy/d except for group “I(ADT),” equal to 0.2 Gy/d. The bootstrap median values of T_{prolif} were included in the range of 18–40 days, reaching the 40 days value for the groups “I(ADT)” and “A(ADT)” in correspondence of the maximum bootstrap median value of d_{prolif} .

DISCUSSION

The short-term TCP of prostate cancer was calculated using 5y BCFS as function of dose, differentiated for risk class and ADT use. Interestingly, in the study high dimension samples were considered^{12,17–20,22,66,67} (group “All,” $N^1 = 71$ and $M^1 = 92$). Statistically more robust median and 95% CI values based on bootstrap-based cross-validation were evaluated, taking into account the influence of asymmetric parameter distributions.

It was observed that the dose–response curves depend on risk class and ADT. Low risk class (“L,” $N^1 = 13$) showed significantly smaller D_{50} and g_{50} values compared to those of intermediate and high risk groups (“IH,” $N^1 = 37$), 54 ± 5 Gy vs 65 ± 2 Gy ($p < 0.0001$) and 1.4 ± 0.5 vs 1.9 ± 0.4 ($p = 0.002$). Using fewer experimental points, some authors^{12,18,22} obtained higher values of dose–response curve steepness (g_{50}), whereas others lower values.^{20,66,67} Our D_{50} values were similar to those previously reported,^{12,18,22} with differences $< 9\%$.

Interestingly, it was noticed that D_{50} and g_{50} values are lower in ADT patients than in no-ADT ones: 57 ± 5 Gy and 1.1 ± 0.4 in ADT patients (“A(ADT),” $N^1 = 25$) compared to 65 ± 2 Gy and 2.3 ± 0.6 in no-ADT patients (“A(noADT),” $N^1 = 22$), with $p < 0.0001$ and $p = 0.002$. Previous studies failed to demonstrate

Table 2. Patient groups considered in the study

<i>l</i> label	Patients groups	Risk class	ADT	<i>N^l</i> label	<i>M^l</i> label
All	Low or intermediate or high risk patients treated	L or I or H	No or Yes or not specified	71	92
A (no ADT)	Low or intermediate or high risk patients treated without ADT	L or I or H	No	22	28
A (ADT)	Low or intermediate or high risk patients treated with ADT	L or I or H	Yes	25	29
L	Low risk patients	L	No or Yes or not specified	13	22
I	Intermediate risk patients	I	No or Yes or not specified	21	27
I (ADT)	Intermediate risk patients treated with ADT	I	Yes	7	8
H	High risk patients	H	No or Yes or not specified	16	20
H (ADT)	High risk patients treated with ADT	H	Yes	8	10
IH	Intermediate and high risk patients	I or H	No or Yes or not specified	37	47
IH (ADT)	Intermediate or high risk patients treated with ADT	I or H	Yes	15	18

ADT, androgen deprivation therapy; H, high risk; I, intermediate risk; L, low risk.

N^l represents the number of clinical sub data sets of table 1s used in the fit of models 1, 2 and 3. *M^l* is the number of clinical sub data sets of table 1Is correspondent to the patients group *l* used to calculate dose-fractionation radiosensitivity and repopulation parameters.

Figure 2. Bootstrap-based averages and standard deviations of D_{50} (2.a) and g_{50} (2.b) derived for each patient group in Table 2. ADT, androgen deprivation therapy.

Figure 3. The plots of bootstrap-based cross-validated dose-response curve with standard dose scheduling (thick line with experimental points as filled circles) with 95% CI for the groups “L” (low risk—Figure 3.a, “I”) (intermediate risk—Figure 3.b and “H”) (high risk—Figure 3.c) of Table 2. The empty circles are the experimental points with no standard dose scheduling. BCFS, biochemical free survival; CI, confidence interval; EQD, equivalent dose.

the dependence of the dose-response curve steepness on ADT.¹⁹ However according to what is observed in clinical practice, our results confirmed that a combination of ADT with radiotherapy produces major improvements in 5y BCFS.^{26–28,35–37}

Our results showed, in each patient group, lower values of radio-sensitivity (α/β) than those reported in literature for late normal tissue morbidity,^{7,10} suggesting that the use of moderate hypofractionated radiotherapy should be considered in all risk classes.

Figure 4. Bootstrap-based averages and standard deviations of α/β derived for each patient group in Table 2. ADT, androgen deprivation therapy.

Figure 5. The plots of 5 year BCFS obtained from EQD2 against the experimental 5 year BCFS with no standard dose scheduling of the groups “L” (low risk—Figure 5.a, “I”) (intermediate risk—Figure 5.b and “H”) (high risk—Figure 5.c). In the plots there are the bisector, as black continuous line, and the experimental points, as thick filled circles. 5 year BCFS from EQD2 is obtained using the bootstrap-based cross-validated dose-response curve and median value of α/β without any dependence on OTT. The points coming from the bootstrap 95% CI (thin circles) are also shown. BCFS, bio chemical free survival; CI, confidence interval; EQD, equivalent dose.

Without considering any OTT dependence, our best estimation of α/β for all patients (“All”) was 1.4 (95% CI 1.0–1.9) Gy and the median values were between 0.9–1.9 Gy for each group. Even if with fewer experimental points, similar results were reported by other authors with best estimations between 0.6–1.9 Gy,¹⁸ 0.9–2.2 Gy¹⁹ and 0.8–1.7 Gy⁶⁷.

The introduction of OTT dependence produced an increase of the best estimation and amplitude of 95% CI of α/β : 2.2 (95% CI 1.1–3.4) Gy for all patients (“All”); these results were similar to others recently reported, 2.7 (95% CI 1.6–3.8) Gy⁶⁷. It must be noted that other authors assumed $d_{prolif} = 0.31$ Gy/d⁶⁷ based on previous evaluations,^{16,19} whereas we obtained an estimation from data of 0.2 (95% CI 0.0–0.3) Gy/d. The T_{prolif} median values were between 18 and 40 days, against the 31–37 days interval reported by other authors^{16,22} and a 0 lag time considered in another paper.¹⁹ Our d_{prolif} values obtained with no lag time were generally lower than those with $T_{prolif} > 0$ ($p = 0.11$) and the Pearson's r coefficient between the T_{prolif} and the differences of d_{prolif} for the two assumption was equal to 0.72, evidencing a strong correlation. Also, formally testing the hypothesis that $T_{prolif} = 0$ vs > 0 , $p = 0.03$ was obtained. Despite these uncertainties,

considering the more robust d_{prolif} and T_{prolif} median values from bootstrap sampling, our results underlined a limited dependence on repopulation, with a daily dose loss of about a quarter of that observed in oropharyngeal squamous cell carcinomas.¹⁶

Interestingly, there was no advantage on SEE by using a general EQD2–response curve depending on five parameters, instead of on three-parameters excluding d_{prolif} and T_{prolif} (<2%).

Our study has several limitations. First, no specifications about patient radiosensitivity⁶⁸, age, comorbidities, irradiated targets such as pelvic lymph node coverage, irradiation techniques and control procedures of dose delivery, ADT regime^{29–31} as well as intertrials consistency of follow-up protocols on BCFS assessment were done.^{18–20,22,34,40–57}

The use of 5y BCFS is still debated because it has not yet been validated against long-term outcomes. This choice was determined by the largest number of trials reporting it, to have sufficient experimental points for reliable non-linear regressions. Furthermore, short-term ADT may have minor efficacy than long-term ADT.

Secondly, some selection bias could have affected our findings, having considered 11 non-randomized studies along with randomized ones. The synthesized method proposed by other authors,^{20,66,67} based on within-randomized studies comparison only to potentially reduce the effect of studies no-homogeneity, is surely of value, enhancing the role of randomization against systematic bias. This method, however, using a fixed effect model, may reflect in critically way of heterogeneity and of some largely weighted trials if only few randomized studies are available, influencing the best estimation and reducing the amplitude of 95% CI.^{20,66,67} Randomization is a sufficient, but not a necessary condition to avoid selection bias. Our methods, even considering only the 14 randomized trials of Table 1, allowed obtaining comparable results for group ("All") with $D_{50} = 61$ (95% CI 52–65) Gy $p < 0.0001$ and $g_{50} = 1.3$ (95% CI 0.6–2.1) $p = 0.003$ with sample size = 33 and $\alpha/\beta = 1.1$ (95% CI 0.4–2.1) Gy $p = 0.005$ with sample size = 42.

CONCLUSION

Ten patient groups, based on risk class and ADT use, were selected from 25 data sets including a total of 20,310 patients. The tumor response parameters were quantified, validated with bootstrap method and compared with literature data.

A significant reduction of dose–response curve parameters was observed in low risk group and in ADT patients. In all groups, fraction size sensitivity was lower for prostate cancer than for normal-tissue late side-effects, suggesting that the use of moderate hypofractionated radiotherapy should be considered in each risk class. A limited dependence on repopulation was also observed, with a daily dose loss of about a quarter of that observed in oropharyngeal squamous cell carcinomas.

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