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Original Article

Accurate prediction of long-term risk of biochemical failure after salvage radiotherapy including the impact of pelvic node irradiation

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ABSTRACT

Background and purpose: Explainable models of long-term risk of biochemical failure (BF) after post-prostatectomy salvage radiotherapy (SRT) are lacking. A previously introduced radiobiology-based formula was adapted to incorporate the impact of pelvic nodes irradiation (PNI).
Materials and methods: The risk of post-SRT BF may be expressed by a Poisson-based equation including pre-SRT PSA, the radiosensitivity α, the clonogen density C, the prescribed dose (in terms of EQD2, $\alpha/\beta = 1.5$ Gy) and a factor ($1\text{-}B\lambda xPSA$) accounting for clonogens outside the irradiated volume, being λ the recovery due to PNI. Data of 795 pT2-pT3, pN0/pN1/pNx (n = 627/94/74) patients with follow-up $\geq$ 5 ye ars and pre-RT PSA $\leq$ 2 ng/mL were randomly split into training (n = 528) and validation (n = 267) cohorts; the training cohort data were fitted by the least square method. Separate fits were performed for different risk groups. Model performances were assessed by calibration plots and tested in the validation group.
Results: The median follow-up was 8.5y, median pre-SRT PSA and EQD2 were 0.43 ng/mL and 71.3 Gy respectively; 331/795 pts received PNI. The most clinically significant prognostic grouping was pT3b and/or ISUP4-5 versus pT2/3a and ISUP1-3. Best-fit parameters were α_{eff} = 0.26/0.23 Gy^{-1}, C = $10^7/10^7$, B = 0.40/0.97, λ = 0.87/0.41 for low/high-risk group. Performances were confirmed in the validation group (slope = 0.89,R^2 = 0.85). Results suggested optimal SRT dose at 70–74 Gy. The estimated reduction of post-SRT BF due to PNI at these dose values was > 5 % for PSA > 1/>0.15 ng/mL for low/high-risk patients, being > 10 % for high-risk patients with pre-SRT PSA > 0.25 ng/mL.
Conclusion: An explainable one-size-fits-all equation satisfactorily predicts long-term risk of post-SRT BF. The model was independently validated. A calculator tool was made available.
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Growing evidence from both large retrospective series [1–4] and, more recently, randomized trials [5–8] suggests a similar clinical efficacy of "early-salvage" as compared to immediate adjuvant radiotherapy in the case of risk factors (extracapsular extension, positive surgical margins, high Gleason score) at radical prostatectomy. Early salvage radiotherapy (SRT), delivered at the first signs of PSA rise, has recently been suggested, in the EAU-EANM-ESTRO-ESUR-SIOG guidelines [9], as the therapy of choice after prostatectomy, since it significantly reduces the risk of overtreatment when compared to adjuvant irradiation. However, the risk of failure after SRT may be not negligible, being affected by several tumor- and treatment-related factors. Among the former should be included the tumor burden, influencing the prostatic specific antigen (PSA) value at irradiation (pre-RT PSA), the

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intrinsic biological aggressiveness of residual cells persisting after surgery as indicated by the Gleason score (from 2016 expressed as ISUP Classes), the PSA kinetics, well described by the doubling time (PSADT), as well as the pT stage and surgical margins status [10–16]. The combination of several adverse prognostic factors permits the identification of different risk classes among patients considered as candidates for SRT [10–12,16,17].

Among the treatment-related factors possibly influencing the clinical outcome of patients treated with SRT, radiation dose should be mentioned [18–21]. Several authors have attempted to model the effect of a moderate dose escalation in the context of SRT by introducing radiobiological concepts for the prediction of the risk of post-SRT biochemical recurrence [18,22]. Ohri *et al.* [22] first suggested a Poisson-based radiobiological model by combining pre-RT PSA, assumed to be a surrogate for the number of clonogens, and the prescribed dose. More recently, our group extended this approach to a model based on a "one-size-fit-all" TCP-based formula [23] incorporating the risk of post-SRT biochemical failure (BF) deriving from the presence of tumor cells outside the volume irradiated, leading to a significant fraction of relapses regardless of the delivered radiation dose. The model was able to fit the risk of 5-year BF of a large multi-institute cohort of node-negative patients previously treated with adjuvant or salvage intent: the resulting best-fit parameters were consistent with previous radiobiological knowledge [24].

In addition, interest in the inclusion of pelvic nodal area in the salvage setting has grown over the last decade, leading many Institutions to add pelvic node irradiation (PNI) to that of the prostatic bed (PB) in men considered at higher risk of post-SRT clinical failure. The first positive findings of a randomized Phase III trial testing the impact of PNI in the salvage setting were recently reported [21].

A national multi-institute collaborative group enrolled up to the end of 2021 patients in a longitudinal observational trial aimed at the prediction of radiation-induced toxicity from irradiation including PNI in the treatment of prostate cancer (ClinicalTrials.gov identifier NCT2803086 [25,26]). Within this group, data relative to the clinical outcome of patients treated with SRT in nine Institutions were also collected, with the following aims:

1. Extending the previously developed model to include PNI impact.
2. Training and validating the best-fit parameters of the model in a large cohort of patients treated with salvage radiotherapy with modern technology and optional use of PNI.
3. Making available to the scientific community a calculator tool for the personalized prediction of the risk of long-term post-SRT BF on the basis of very few baseline clinical data, the prescribed dose and the use of PNI.

Materials and methods

Modeling the risk of biochemical relapse by a Poisson-based TCP model

Our model [23] to predict the risk of BF after post-prostatectomy radiotherapy is based on: (1) Poisson-statistics for the probability of clonogen sterilization [27–29]; (2) the assumption that the initial number of clonogens N_0 is proportional to the pre-SRT PSA value [22,24]; (3) the assumption that minimal risk of BF after post-prostatectomy radiotherapy is never equal to zero, since a fraction of patients may experience BF owing to the presence of clonogens outside the irradiated volume [22]; (4) the time factor (i.e. repopulation) may be ignored in first approximation. Under these assumptions, biochemical relapse-free survival at a certain time may be predicted by the equation:

$$\mathrm{bRFS} = \mathrm{K}(1 - \exp(-\alpha_{\mathrm{eff}}\mathrm{D}))^{\mathrm{C}\times\mathrm{PSA}} \quad (1)$$

where PSA is the pre-SRT PSA value, D the delivered 2-Gy equivalent dose, α_{eff} the effective radiosensitivity parameter, C the number of cells corresponding to a pre-SRT PSA value of 1 ng/mL, and K the minimal obtainable risk of BF, ranging between 0 and 100 %. Formula (1) is biased by the fact that the parameter K is fixed, possibly representing an excessively hard constraint; a further limitation is the assumption that radiosensitivity is identical for all patients. As the parameter K is expected to depend critically on pre-SRT PSA, in a preliminary approximation we arbitrarily assumed K to depend linearly on PSA at SRT start. Thus, formula (1) became [23]:

$$\mathrm{bRFS} = (1 - \mathrm{B}\times\mathrm{PSA}) \times (1 - \exp(-\alpha_{\mathrm{eff}}\mathrm{D}))^{\mathrm{C}\times\mathrm{PSA}} \quad (2)$$

The parameter B represents the increasing risk of BF due to clonogens outside the irradiated volume for a PSA value at irradiation equal to 1 ng/mL.

In the current investigation, the formula (2) was modified in order to incorporate the possible role of PNI by the introduction of the parameter λ, corresponding to the expected reduction of post-SRT BF deriving from PNI (equal to 0 without PNI):

$$\mathrm{bRFS} = (1 - \mathrm{B}\times\lambda\times\mathrm{PSA}) \times (1 - \exp(-\alpha_{\mathrm{eff}}\mathrm{D}))^{\mathrm{C}\times\mathrm{PSA}} \quad (3)$$

Patient population

This retrospective study was approved by the IRB of the Coordinating Institute (#175/INT/2021). Criteria for inclusion were:

1. Patients previously submitted to prostatectomy and treated with salvage radiotherapy due to PSA rise, and without evidence of metastatic disease at SRT start;
2. minimum follow-up of 5 years;
3. pre-SRT PSA value $\leq$ 2 ng/mL.

A cohort of 795 patients satisfying the inclusion criteria and treated in nine Institutes in the period 2000–2016 was available for the fit. Most patients (58 %) were treated with IMRT static or rotational (VMAT/Tomotherapy): Daily IGRT was used in about half of patients (49 %) using Tomotherapy MVCT or CBCT while for the remaining patients weekly EPID/portal films checks were mostly performed. The end-point was post-SRT BF, defined as a single PSA $\geq$ 0.20 ng/mL after post-radiotherapy nadir or a continued rise of PSA despite SRT [15]. Given the long follow-up and the timing of post-SRT BF, the crude incidence was considered as representative of the cumulative long-term risk of BF.

The assessment of the possible presence of metastatic disease were generally performed by conventional staging, including in most cases CT and bone scans, with only a minority of patients undergoing choline or PSMA PET. A large number of clinical and treatment related data were collected (Table 1). The 2-Gy equivalent radiation dose (EQD2, for α/β = 1.5 Gy) was used in place of D in formula (3).

According to TRIPOD, level 2 [30], the cohort was randomly split into two groups (training and validation), approximately equal to 2/3 and 1/3 of the total. Data for the training group (n = 528) were fitted with the model (see below for details) and its performances were tested in the validation group (n = 267). Patient characteristics are summarized in Table 1.

Grouping patients in "low-" and "high-" risk subsets

A preliminary univariable logistic analysis was performed to investigate which clinical and treatment-related factors were associated with the risk of post-SRT BF. Variables with a p-value < 0.20 were entered into a multivariable logistic model using backward

Table 1
Patient characteristics.

Characteristic	
Age at SRT (years)	Median: 68 IQR: 64–72
Pre-SRT PSA (ng/mL)	Median: 0.43 Range: 0.1–2.0 IQR: 0.24–0.81
pT stage	
pT2	490 (61.6 %)
pT3a	225 (28.3 %)
pT3b	80 (10 %)
pN stage	
N0	627 (78.9 %)
N1	94 (11.8 %)
NX	74 (9.3 %)
Number of removed Lymph nodes	Median: 11 IQR: 8–16
Pelvic Node Irradiation (PNI)	331 (42 %)
Concomitant/Adjuvant ADT	311 (39 %)
ADT duration (months)	Median:14.4 IQR: 9–25
Time from surgery to SRT (years)	Median:3 IQR: 1–5
SRT dose (EQD2 (α/β = 1.5), Gy)	Median 71.3 IQR: 70–72.4
PNI dose (EQD2 (α/β = 1.5), Gy)	Median: 48.4 IQR: 48.4–50.3
ISUP grading	
1	265 (33.3 %)
2	249 (31.3 %)
3	164 (20.6 %)
4	63 (7.9 %)
5	54 (6.7 %)

Abbreviations: SRT = Salvage Radiation Therapy; ADT = Androgen Deprivation Therapy.

stepwise regression. Results are summarized in the Supplementary Data.

According to these findings, the most informative clinical predictors were pT stage and ISUP grouping, in addition to EQD2, pre-SRT PSA and PNI, which were already included in the model. Of note, positive lymph-nodes, time between surgery and SRT and hypofractionation, significantly associated with BF in univariable analysis, were not retained at multivariable analysis. As different radiosensitivities and propensities to regional/metastatic spread according to both of these parameters may be expected once fixed pre-SRT PSA, dose and PNI (yes/no) are fixed, patients were grouped accordingly. Different groupings were investigated, leading to different fittings; the results are summarized in the Supplementary Data. The grouping that best discriminated the two patient subsets at lower and higher risk of post-SRT BF at multivariable analysis was: "low risk"=pT2/pT3a and ISUP 1–3 *vs* "high risk"= pT3b and/or ISUP 4–5.

Fitting procedures and quality of fit assessment

Formula (3) was applied to the two sub-groups separately to derive the best-fit values of the parameters. Fit was performed using the Least Square method: the best-fit parameters were chosen by minimizing the summed square of residuals. The residual for the i-th data point r_i is defined as the difference between the observed response value y_i and the fitted response $\widehat{y_i}$:

$$r_i = y_i - \widehat{y_i}$$

The summed square of residuals is given by:

$$S = \sum_{i=1}^{n} r_i^2 = \sum_{i=1}^{n} \left(y_i - \widehat{y_i}\right)^2$$

where n is the number of patients included in the fit and S is the sum of squares error estimate.

The optimization was performed with the Curve Fitting Toolbox in Matlab 2020b version using custom Eq. (3). By default, the 95 % confidence intervals (CI) were evaluated from the sum of squares error (SSE) calculated as the square root of the diagonal elements of the estimated values, assuming that errors are normally distributed. Some constraints were defined during the fitting procedure. B and λ were set to be >0 and $\leq$1; based on data from the literature [22,24,28], α_{eff} was constrained within the range 0.23–0.28 Gy^{-1}. C, the number of clonogens corresponding to a PSA value of 1 ng/mL, was fixed to 10^7, according to our previous results [23]; different values were reported in literature, generally ranging between 10^6 and 10^9 [22,24,28–31], although this parameter is much less critical in fitting data when compared to α_{eff}. In order to better assess the values of B and λ, limiting any risk of interplay between their values, the fit followed a two-step procedure: first, data for the high and low risk groups were separately fitted considering only patients without PNI, fixing λ = 1. For each subgroup (high and low risk), data referred to patients treated with PNI were then fitted to assess the best value of λ by fixing α_{eff} and B values obtained by the previous fitting of no-PNI data.

Validating model performance

Goodness-of-fit was assessed by the calibration plot and the Hosmer and Lemeshow (H&L) test. Medcalc v.12 (Medcalc software bvba, Mariakerke, Belgium) and R software (R 2.15.2 software, http://www.R-project.org) were used for analyses.

Internal validation was carried out by means of a cross-validation approach: the model resulting from the fit realized in the training group was tested in the validation group, and calibration plots referring to the two groups were considered to assess the robustness of the resulting model: slope and R^2 values were considered to assess the goodness of fit, and to compare performances in the two cohorts.

To corroborate the results, the previously described validation procedure was repeated 10 folds, in order to quantify the impact of the random choice when splitting the population in training and validation cohorts. The resulting best fit values of the parameters, slope and R^2 values were then reported.

Model predictions and dose–effect curve

Once the best fit values of the parameters were assessed, the predictions resulting from Eq. (3) were plotted for the two risk groups against the prescribed EQD2. Plots were made for different pre-SRT PSA values, with and without PNI irradiation.

Results

The median follow-up was 8.5 years (interquartile range, IQR: 6.5–11.5); the median pre-RT PSA was 0.43 ng/mL (IQR:0.24–0.81); 259 patients experienced a post-SRT BF after a median interval of 3.1 years (IQR:1.6–5.6) from SRT start, while a clinical relapse, local and/or distant, was observed in 141 patients after a median of 5.3 years (IQR: 2.5–8.0).

The fit converged in all the analyzed scenarios: only the performances of the model showing the greatest benefit from PNI are presented in the main text, while the remaining results are reported in the Supplementary Materials.

The best fit values of the model parameters with their 95 % confidence intervals for both the low- and high-risk subsets are reported in Table 2.

The calibration plot showed good agreement between predicted and expected values (slope: 0.88, R^2: 0.77). Performances were

Table 2
best fit values of the model parameters with their 95% C.I. for low- and high-risk cohorts.

Subgroup	α (Gy^{-1})	B	C	λ
pT2/pT3a and ISUP 1–3	0.26	0.40	10^7	0.87
pT3b and/or ISUP 4–5	0.23	0.97	10^7	0.41

confirmed in the validation group (slope: 0.89, R^2: 0.85), as shown in Fig. 1.

The tenfold exercise (shown in the Supplementary Materials) confirmed the robustness of the results, showing limited variations of the model's parameters as well as of slopes and R^2 values: as an example, the slope for training and validation groups were in the ranges 0.82–0.92 and 0.83–0.92 respectively.

The results relative to different groupings are shown in the Supplementary Materials: all models showed moderate/good calibration (slope: 0.89–0.90 R^2: 0.72–0.89). Goodness of fit was confirmed in all cases by H&L test ($p > 0.05$).

The corresponding risk of post-SRT BF *vs* prescribed EQD2 for different pre-RT PSA values and for the high- and low-risk groups are plotted in Figs. 2 and 3. Curves are shown for a few representative PSA values and for PB only and PB + PNI irradiation (continuous/dotted lines).

Discussion

The evidence of a dose–effect in post-prostatectomy radiotherapy was first claimed by King and Kapp [18] relying on data published in the early 2000 s. In addition, the evidence that post-SRT clinical outcome is strongly influenced by the pre-SRT PSA value led researchers to postulate PSA as a robust surrogate for the number of clonogens [28]. Ohri *et al.* [22] first fitted the published data from a Poisson-based radiobiological model by combining pre-SRT PSA and SRT dose. Fiorino *et al.* [23] extended the original Ohri model to explicitly include the differential risk of distant relapse, not directly affected by the delivered dose, and the different expected radiosensitivity according to the tumoral Gleason score at prostatectomy. This model proved to adequately fit individual clinical data from a large multi-Institute cohort of patients treated with both adjuvant and salvage radiotherapy. Importantly, the best-fit values of the parameters were consistent with values reported in both the radical setting and in in-vitro studies [24,28].

The current study incorporated the impact of PNI in a multi-Institute cohort of patients treated with modern technology, high-dose and early SRT. As a consequence, the resulting best-fit parameters should better represent the current real-life scenario, providing the clinician with a reliable tool for the individual prediction of long-term risk of BF after SRT. Very importantly, the resulting model fitted the data with excellent calibration, and performances were replicated in a validation group obtained by splitting the original population.

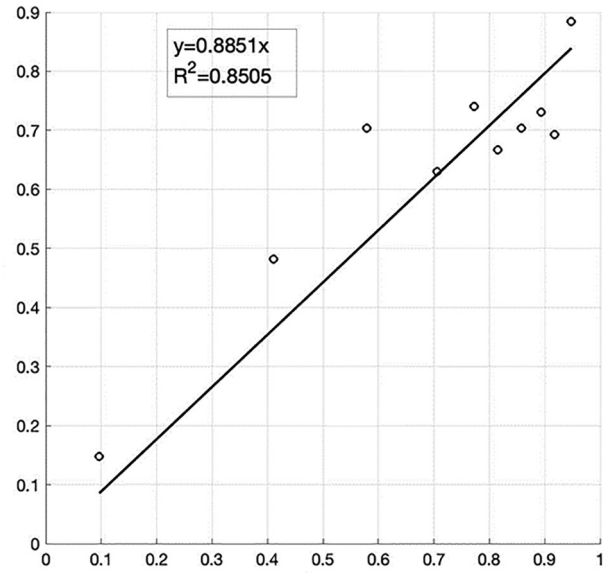

Fig. 1. Performances of the model in the validation group: calibration plot.

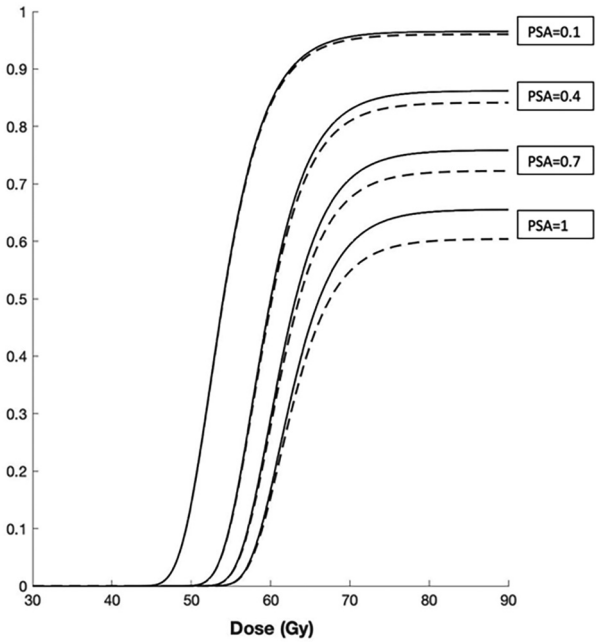

Fig. 2. Long-term biochemical failure (8.5y, median follow-up, minimum: 5y) dose–effect curve for different PSA values before salvage Radiotherapy: "low-risk" group (pT2/pT3a and ISUP 1–3).

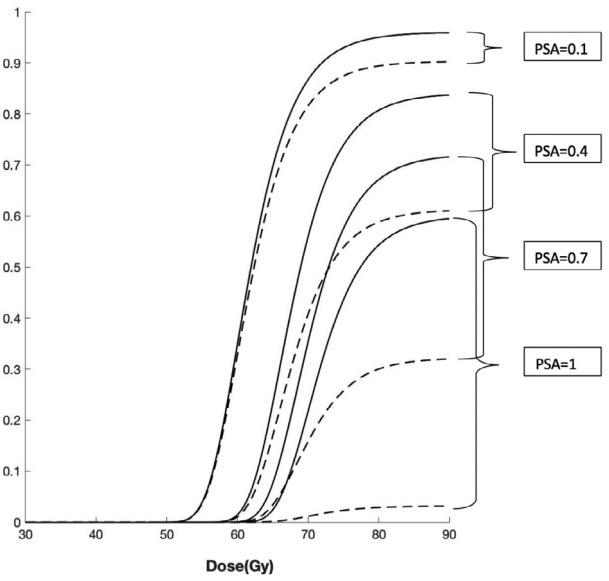

Fig. 3. Long-term biochemical failure (8.5y, median follow-up, minimum: 5y) dose–effect curve for different PSA values before salvage Radiotherapy: "high-risk" group (pT3b and/or ISUP 4–5).

Impact of SRT dose

Results relative to dose–effect indicate that little gain could be expected from dose escalation to the prostatic bed roughly above 70 Gy for low-risk (pT2/pT3a and ISUP Class 1–3) and 74 Gy for high-risk (pT3b and/or ISUP Class 4–5) patients. On the other hand, the minimum risk of post-SRT BF (corresponding to the plateau of Figs. 2–3) is heavily dependent on pre-RT PSA, pT stage and ISUP, and cannot be further diminished by increasing the dose. This is in quite good agreement with several investigations [18,19,23], although a recent randomized trial failed to demonstrate an improvement when escalating the dose from 64 to 70 Gy [32]. Several motivations may be claimed to try to explain this result such as the possible inadequacy of the sample size as the result of a likely too optimistic estimate of the expected gain of 6 Gy dose escalation, the low median PSA value (0.35 ng/mL) of the population and the prevalence of low-risk patients, according to our current definition. As a matter of fact, as shown in Fig. 2, the gain expected by our model from a dose escalation from 64 to 70 Gy in low risk patients with PSA values between 0.1 and 0.4 ng/ml (without PNI) is expected to be in the range of 1–5 %, which is not in contrast with the apparent negative result of this trial.

Out-of-field relapses and impact of PNI

As also reported by Tendulkar *et al.* [33], a dramatic inverse relationship exists between pre-SRT PSA values and risk of post-SRT biochemical failure, especially for values above 0.4–0.5 ng/mL, and is far more pronounced for the high-risk group. In Fig. 4, as an example, the long-term freedom from biochemical failure corresponding to a hypothetical delivered dose of 70 and 74 Gy for low- and high-risk patients, respectively, are plotted against pre-SRT PSA values in the range 0.01–1 ng/mL and with/without PNI.

These findings corroborate, if necessary, the concept that SRT should be delivered at the first evidence of PSA rise after prostatectomy [9].

The impact of PNI in the context of early SRT was found to be quite limited for the majority of low-risk patients. On the other hand, its role became clinically meaningful for high-risk patients even at relatively low pre-RT PSA values. Considering an arbitrary minimal threshold of 5 % for diminished risk of BF deriving from PNI, pelvic nodal-area irradiation would be advisable for pre-SRT PSA values >1 ng/ml for the low-risk cohort, but still above 0.15 ng/mL for the high-risk patients. Importantly, for high-risk patients, a gain in the range of 25 % in terms of post-SRT biochemical control may be expected for pre-SRT values $\geq$0.5 ng/mL. Our prediction seems to be quite consistent with the recently reported findings of the RTOG0534 SPPORT trial [21], regarding the positive impact of PNI. On the other hand, the different (and systematic) administration of ADT for 4–6 months in the experimental arms of that trial makes any comparison impossible when considering the impact of ADT. Importantly, our model clearly suggests that the beneficial role of PNI depends on several factors and could be expected to be negligible in the majority of patients in the era of early SRT. This suggests the need of personalization of PNI prescription despite the positive findings of the SPPORT trial that could be due to the combination of a large effect in the "high-risk" group and a little or negligible effect in the "low-risk" subset.

Study limitations

Our study is not devoid of limitations. The availability of a (substantially) larger number of patients would have permitted a further refining of the prediction, through multiple stratifications. On the other hand, the current separation into only two classes

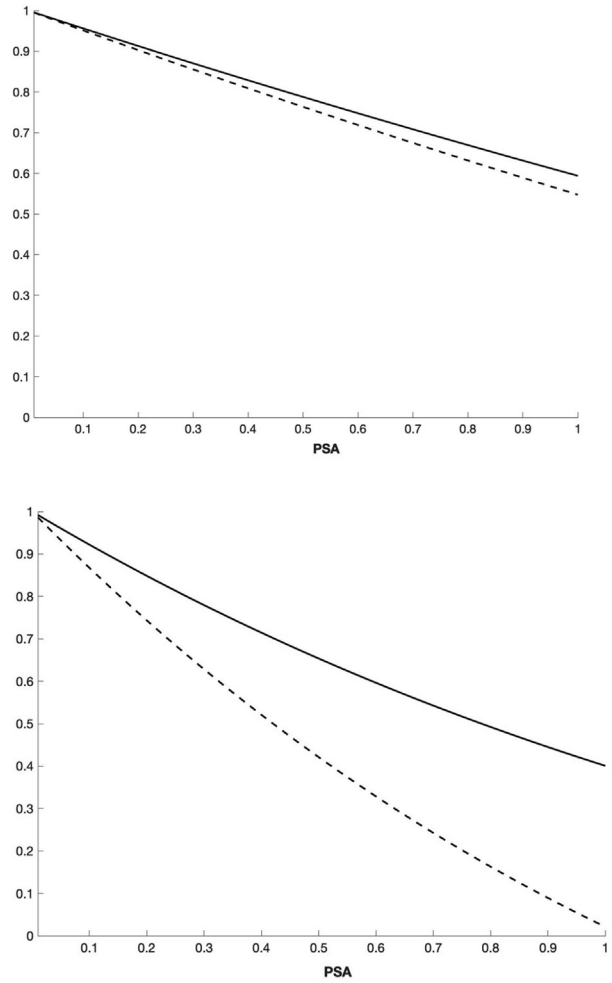

Fig. 4. Relationship between long-term biochemical failure (8.5y, median follow-up, minimum: 5y) and PSA value before salvage Radiotherapy with and without pelvic node irradiation (PNI): in the upper part, it refers to the "low-risk" group (pT2/pT3a and ISUP 1–3) with a prescribed dose of 70 Gy; in the lower part, it refers to the "high-risk" group (pT3b and/or ISUP 4–5) with a prescribed dose of 74 Gy.

has the benefit of maintaining the formalism that is easily understood and robust in terms of use. The good performance, even in the validation cohort, showed that this choice is a good compromise, offering consistent and reasonably explainable values for all parameters involved, as well as good predictive accuracy. The merging of real-life multi-centric data also makes the model likely to be generalizable. On the other hand, the choice of the crude incidence of biochemical failure has also some uncertainty due to the unavoidable loss of a fraction of events due to the variable follow-up time between patients. This choice was justified by the opportunity of exploiting a large database with long follow-up: it is also important to underline that the spread of the time-to-event (IQR: 1.6–5.6 years) compared to the follow-up (IQR: 6.5–11.6 years) is consistent with the detection of the very large majority of biochemical failures in this population.

The uncertainty concerning the assessment of EQD2 for patients treated with moderate hypo-fractionation could be an issue. The choice to use a low alpha/beta value (1.5 Gy), according to the majority of authors, has some degree of arbitrariness as no clear confirmation exists in the case of residual cells after prostatectomy, even though a different radiosensitivity of residual prostate cancer cells after surgery when compared to that of the intact prostate is unlikely. Other limitations such as the

lack of centralized ISUP review and the limits of a mainly conventional only pre-irradiation staging due both to inter-Institute variability and to the time span analyzed have to be mentioned.

The lack of impact of Hormonal therapy

Another limitation concerns the impossibility of adequately incorporating any role for androgen deprivation therapy (ADT) in the model, in part as a result of the heterogeneity and duration of the treatments, and probably of the fact that ADT was prescribed in less than one third of the patients. As shown in the Supplementary Materials, ADT did not emerge among the major predictors of post-SRT BF. On the other hand, some impact of hormonal therapy on specific subsets of patients cannot be excluded.

In order to better investigate the impact of ADT on the goodness of the model and to avoid any doubt regarding potential biases due to possible association between ADT and PNI, several additional analyses were performed and results are fully reported in the Supplementary Materials:

(a) The BRF survival curves were added for the whole population and for the two groups (with and without PNI) by stratifying patients according to ADT administration. In all cases, the log-rank tests showed no impact of ADT.
(b) The association between ADT administration and PNI was quite poor (Spearman test, Mann-Withney test: $p > 0.20$) with 59 % of patients treated with PNI not receiving ADT.
(c) As a result of points a) and b) (in addition to the results of the multivariate analysis), it clearly emerges that PNI was not a surrogate of the use of ADT.
(d) In order to identify any impact of ADT on the accuracy of our model, calibration curves for the two populations of patients receiving or not ADT were generated. Results showed similarly good calibration for the two groups clearly suggesting that ADT has not any major impact.

This result is not in contradiction with the recently reported positive impact of concomitant and short-term ADT [21] and has not to be considered indicative of the uselessness of ADT in addition to salvage radiotherapy.

Conclusions

An explainable one-size-fits-all equation satisfactorily predicts the long-term risk of biochemical failure after SRT. The model parameters were obtained by fitting a large multi-centric cohort, and the model was independently validated. Once a sufficiently high radiation dose (EQD2: 70–74 Gy) has been delivered, the fraction of relapsing patients will not be reduced by further dose escalation to the prostatic bed. The individually estimated impact of PNI depends on pre-RT PSA, pT stage and ISUP Class, and seems to be significant in the case of pT3b and/or ISUP 4–5 disease, linearly increasing for rising pre-RT PSA values but remaining quite low for pT2-pT3a and/or ISUP 1–3 disease. A better refinement of the prediction – especially in better discriminating subtle differences between pT2 and pT3a and between ISUP 1–2 and 3 – may be expected by substantially increasing the number of patients to be considered for the fit. A larger population and an even more prolonged follow-up would permit the extension of this modeling also to "harder" clinical endpoints, such as clinical failure and death.

A calculation tool for the individual prediction of the expected long-term risk of post-SRT BF for different pT stages, ISUP Classes and pre-SRT values, with or without PNI, was realized and is available upon request to the authors. The identification of new biomarkers, such as genomic classifiers or image-based biomarkers could further improve the accuracy of individual prediction of BF.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.08.001.

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