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Prediction of Outcome Following Early Salvage Radiotherapy Among Patients with Biochemical Recurrence After Radical Prostatectomy

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Abstract

Background: Early salvage radiotherapy (eSRT) represents the only curative option for prostate cancer patients experiencing biochemical recurrence (BCR) for local recurrence after radical prostatectomy (RP).
Objective: To develop and internally validate a novel nomogram predicting BCR after eSRT in patients treated with RP.
Design, setting, and participants: Using a multi-institutional cohort, 472 node-negative patients who experienced BCR after RP were identified. All patients received eSRT, defined as local radiation to the prostate and seminal vesicle bed, delivered at prostate-specific antigen (PSA) $\leq$0.5 ng/ml.
Outcome measurement and statistical analysis: BCR after eSRT was defined as two consecutive PSA values $\geq$0.2 ng/ml. Uni- and multivariable Cox regression models predicting BCR after eSRT were fitted. Regression-based coefficients were used to develop a nomogram predicting the risk of 5-yr BCR after eSRT. The discrimination of the nomogram was quantified with the Harrell concordance index and the calibration plot method. Two hundred bootstrap resamples were used for internal validation.
Results and limitations: Mean follow-up was 58 mo (median: 48 mo). Overall, 5-yr BCR-free survival rate after eSRT was 73.4%. In univariable analyses, pathologic stage, Gleason score, and positive surgical margins were associated with the risk of BCR after eSRT (all $p \leq 0.04$). These results were confirmed in multivariable analysis, where all the previously mentioned covariates as well as pre-RT PSA were significantly associated with BCR after eSRT (all $p \leq 0.04$). A coefficient-based nomogram demonstrated a bootstrap-corrected discrimination of 0.74. Our study is limited by its retrospective nature and use of BCR as an end point.
Conclusions: eSRT leads to excellent cancer control in patients with BCR for presumed local failure after RP. We developed the first nomogram to predict outcome after eSRT. Our model facilitates risk stratification and patient counselling regarding the use of secondary therapy for individuals experiencing BCR after RP.
Patient summary: Salvage radiotherapy leads to optimal cancer control in patients who experience recurrence after radical prostatectomy. We developed a novel tool to identify the best candidates for salvage treatment and to allow selection of patients to be considered for additional forms of therapy.

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1. Introduction

Radical prostatectomy (RP) is a treatment option for patients with clinically localised prostate cancer (PCa) [1,2]. However, biochemical recurrence (BCR) has been reported in up to 40% of men treated with surgery at long-term follow-up [1,2]. Although BCR does not invariably translate into systemic progression and death, patients with recurring disease are at a higher risk of developing distant metastases and experiencing cancer-related mortality [3,4]. Among treatment modalities for patients with BCR, salvage radiotherapy (SRT) currently represents the recommended option for men with presumed or documented local failure [5–17]. The efficacy of SRT is highly dependent on the prostate-specific antigen (PSA) level at the time of treatment [7–17]. For this reason, SRT should be ideally administered early, at the first sign of PSA recurrence [5,6,18]. Nevertheless, even when timely RT is provided, a proportion of patients will experience subsequent progression [18]. Identifying these individuals is crucial because they may harbour micrometastatic disease and therefore benefit from more extensive salvage treatments. For these reasons, predictive models are needed to identify men at higher risk of progression after early salvage radiotherapy (eSRT). This is even more important considering the lack of sensitivity of currently available imaging modalities to distinguish between local and distant recurrence at low PSA levels [19].

Although previous studies have evaluated predictors of BCR after SRT [7–17], virtually all these series included a substantial proportion of patients treated at higher PSA levels (>0.5 ng/ml). Consequently, these data may not be generalizable to contemporary patients treated with SRT at the earliest sign of disease progression. To address this void, we sought to develop a model predicting BCR after eSRT. This predictive tool might help clinicians to identify the best candidates for SRT at low levels of PSA recurrence, and it might likewise be useful to select those patients unlikely to experience a durable response to eSRT who might be managed with more extensive salvage treatments.

2. Materials and methods

2.1. Study population

After ethical committee approval from each participating centre, 766 patients who received eSRT for BCR after RP and pelvic lymph node dissection for nonmetastatic PCa at seven tertiary care centres between February 1993 and April 2009 were identified. All patients had histologically confirmed pT2/pT3, R0–R1, pN0 disease at RP. All patients had undetectable PSA after surgery with a subsequent detectable PSA level that increased on two or more laboratory determinations, according to the definition of BCR after RP provided by the National Comprehensive Cancer Network Guidelines [20]. No patient received neoadjuvant or adjuvant hormonal therapy. ESRT was defined as RT administered for a PSA ≤0.5 ng/ml at the time of eSRT, per current guidelines recommendations [5]. Patients with unknown preoperative PSA, unknown pathologic stage, unknown pathologic Gleason score, and unknown radiotherapy (RT) dose were excluded from the current analyses (n = 294). This resulted in a final population of 472 patients.

2.2. Radiotherapy technique

RT was defined as local radiation to the prostate and seminal vesicle bed. All patients were treated with high-energy photon beams (10–25 mV) at conventional fractionation (1.8–2 Gy per fraction), with a median dose of 66.6 Gy (interquartile range [IQR]: 66.6–70.2). Conventional nonconformal treatment was delivered, and rectangular or minimally blocked beams were used. Alternatively, a three-dimensional conformal approach was used: The clinical target volume (CTV) was delineated on computed tomography (CT) images and included the prostatic fossa and periprostatic tissue. Clinical findings, presurgery CT scan, and surgical clips guided the clinicians in defining CTV. The planned target volume was defined as CTV plus a 0.8- to 1-cm margin to account for organ motion and setup error. No patient received hormonal treatment during eSRT.

2.3. Covariates and end points

Age at surgery and at RT, preoperative PSA level, total dose of RT delivered, pathologic stage, pathologic Gleason score, surgical margins, time from surgery to eSRT, and pre-RT PSA were considered. Recurrence after eSRT was defined as two consecutive PSA values ≥0.2 ng/ml. Follow-up time was defined as time between the initiation of eSRT and BCR or last follow-up.

2.4. Statistical analyses

Means, medians, and IQRs were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The t test and chi-square test were used to compare the statistical significance of differences in means and proportions, respectively.

Statistical analyses consisted of different steps. First, the Kaplan-Meier methodology was used to assess the BCR-free survival rates after eSRT in the overall population, as well as according to pathologic Gleason score, pathologic stage, and surgical margin status. The log-rank test was used to compare the 5-yr BCR-free survival rates by patient categories. Second, uni- and multivariable Cox proportional hazards regression analyses to assess features associated with BCR after eSRT were computed. Variables tested included preoperative PSA, pathologic Gleason score, pathologic stage, surgical margin status, time from RP to eSRT, pre-RT PSA, as well as total RT dose. Third, multivariate regression coefficients of the independent predictors of BCR after eSRT were then used to develop a nomogram predicting the probability of BCR at 5 yr after eSRT. Internal validation of the nomogram was performed using 200 bootstrap resamples to calculate an unbiased measure of its ability to discriminate among patients [21,22]. The Harrell concordance index was used to assess discrimination and expressed as a value between 0.5 and 1.0, where 1.0 indicates perfect prediction and 0.5 is equivalent to a toss of a coin. Subsequently, the relationship between the nomogram predicted probability and the observed fraction of patients experiencing BCR at 5 yr after eSRT was graphically depicted in the calibration plot. Finally, a decision curve analysis was performed to evaluate the net benefit associated with the use of our model [23].

All statistical tests were performed using the R statistical package v.3.0.2, with a two-sided significance level set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

Table 1 summarises the baseline descriptive characteristics of the 472 patients included in the study. When patients were stratified according to BCR after eSRT, significant differences were recorded with respect to preoperative PSA,

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Table 1 – Descriptive characteristics of patients treated with early salvage radiotherapy (eSRT) for biochemical recurrence (BCR) after radical prostatectomy for prostate cancer, stratified according to the occurrence of BCR during follow-up after eSRT

	Overall $n = 472$	Patients who did not experience BCR during follow-up $n = 362$ (76.2%)	Patients who experienced BCR during follow-up $n = 110$ (23.3%)	p value
Age at surgery, yr				
Mean (median)	62.3 (63)	62.3 (63)	62.1 (63)	0.7
IQR	58–66	58–66	58–66	
Preoperative PSA, ng/ml				
Mean (median)	11.3 (8.4)	10.2 (8.1)	14.6 (10.1)	<0.001
IQR	5.6–12.6	5.4–11.4	6.0–15.8	
Pathologic T stage (%)				
pT2	217 (46.0)	175 (48.3)	42 (38.2)	0.1
pT3a	170 (36.0)	123 (34.0)	47 (42.7)	
pT3b	85 (18.0)	64 (17.7)	21 (19.1)	
Surgical margin status (%)				
Negative	237 (50.2)	193 (53.3)	44 (40.0)	0.01
Positive	235 (49.8)	169 (46.7)	66 (60.0)	
Pathologic Gleason score (%)				
≤6	210 (44.5)	182 (50.3)	28 (25.5)	<0.001
7	184 (39.0)	129 (35.6)	55 (50.0)	
≥8	78 (16.5)	51 (14.1)	78 (16.5)	
Pre-RT PSA, ng/ml				
Mean (median)	0.24 (0.24)	0.24 (0.23)	0.27 (0.27)	0.01
IQR	0.13–0.35	0.12–0.34	0.17–0.39	
Time from surgery to eSRT, mo				
Mean (median)	32.3 (24.2)	32.2 (24.2)	32.8 (25.0)	0.8
IQR	13.5–43.0	13.8–44.0	13.1–39.2	
Dose of radiotherapy, Gy				
Mean (median)	67.9 (66.6)	68.0 (66.6)	67.5 (66.6)	0.1
IQR	66.6–70.2	66.6–70.2	66.6–66.6	

BCR = biochemical recurrence; eSRT = early salvage radiotherapy; IQR = interquartile range; PSA = prostate-specific antigen; RT = radiotherapy.

surgical margin status, pathologic Gleason score, and pre-RT PSA (all $p \leq 0.01$). The proportion of patients with pT3 disease was higher among men who experienced BCR compared with their BCR-free counterparts (61.8 vs 51.7%, respectively; $p = 0.05$). Supplemental Table 1 depicts the baseline characteristics of patients who experienced BCR and of those who were BCR free at a follow-up ≥60 mo.

3.2. Kaplan-Meier analyses

Mean and median follow-up was 58.0 mo (95% confidence interval [CI], 51.7–60.6) and 48.0 mo (95% CI, 43.3–59.7), respectively. Overall, 5-yr BCR-free survival rate after eSRT was 73.4% (Fig. 1). When patients were stratified according to pathologic tumour stage, the 5-yr BCR-free survival rates were 80.6%, 65.5%, and 67.0% for men with pT2, pT3a, and pT3b disease, respectively (Fig. 2a; for comparison of patients with pT2 vs pT3a and pT2 vs pT3b, $p < 0.05$; for comparison of patients with pT3a vs pT3b, $p = 0.9$). When patients were stratified according to pathologic Gleason score, the 5-yr BCR-free survival rates were 85.3%, 66.6%, and 58.8% for men with Gleason score ≤6, 7, and 8–10, respectively (Fig. 2b; $p < 0.001$). Finally, the 5-yr BCR-free survival rates were 78.8% and 68.2% for men with negative and positive surgical margins, respectively (Fig. 2c; $p = 0.04$).

3.3. Cox regression analyses

Table 2 shows uni- and multivariate Cox regression analyses testing the association of various clinicopathologic demographics and patients' risk of BCR after eSRT. In univariate analyses, higher pathologic tumour stage, positive surgical margins, and higher pathologic Gleason score were significant predictors of BCR after eSRT (Table 2; all $p \leq 0.04$). These results were confirmed in multivariate

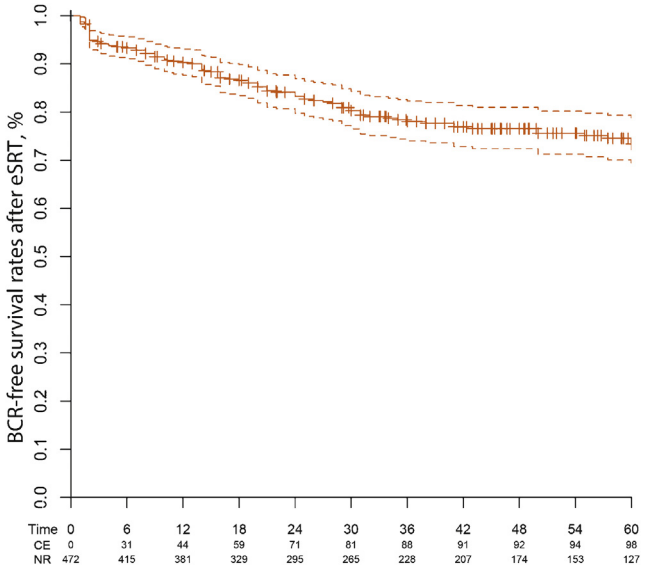

Fig. 1 – Kaplan-Meier curve depicting biochemical recurrence (BCR)-free survival in 472 patients affected by prostate cancer receiving early salvage radiotherapy for BCR after radical prostatectomy.
CE = cumulative events; eSRT = early salvage radiotherapy; NR = number at risk.

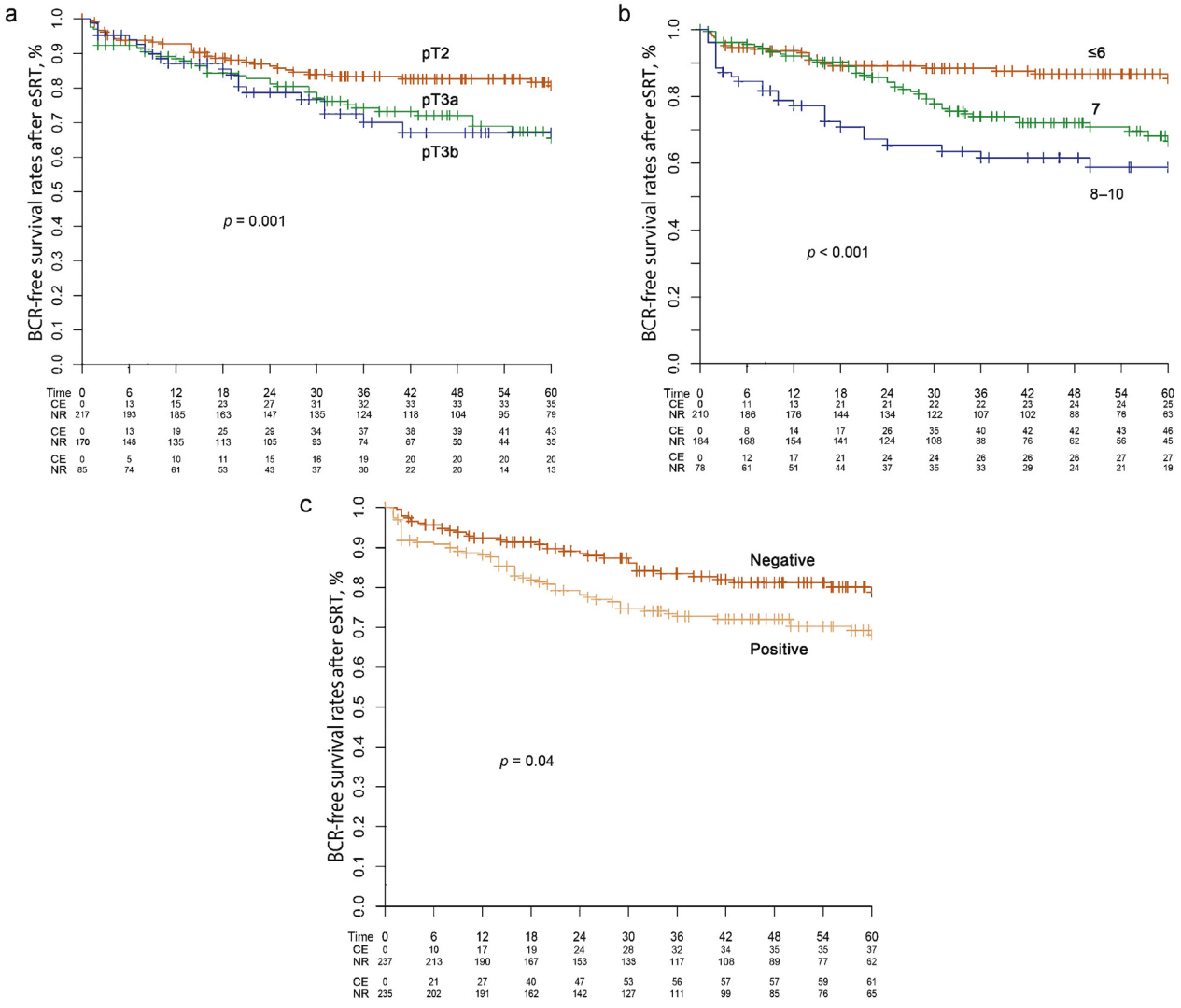

Fig. 2 – Kaplan-Meier curve depicting biochemical recurrence–free survival after stratifying patients according to (a) pathologic stage, (b) pathologic Gleason score, and (c) surgical margins.
BCR = biochemical recurrence; CE = cumulative events; eSRT = early salvage radiotherapy; NR = number at risk.

Table 2 – Uni- and multivariable Cox regression analyses predicting biochemical recurrence after early salvage radiotherapy (eSRT) in 472 patients with prostate cancer undergoing radical prostatectomy and eSRT

	Univariable Cox regression analysis		Multivariable Cox regression analysis			
			Model 1		Model 2	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Pathologic T stage						
pT2	1 (Ref)	–	1 (Ref)	–	1 (Ref)	–
pT3a	1.73 (1.14–2.63)	0.01	1.79 (1.16–2.77)	0.01	1.78 (1.16–2.76)	0.01
pT3b	1.75 (1.03–2.97)	0.04	1.95 (1.11–3.42)	0.02	1.94 (1.11–3.38)	0.02
Surgical margin status						
Negative	1 (Ref)	–	1 (Ref)	–	1 (Ref)	–
Positive	1.53 (1.05–2.24)	0.03	1.62 (1.10–2.39)	0.01	1.63 (1.11–2.40)	0.01
Pathologic Gleason score						
≤6	1 (Ref)	–	1 (Ref)	–	1 (Ref)	–
7	2.29 (1.45–3.62)	<0.001	2.21 (1.39–3.49)	0.001	2.19 (1.39–3.47)	0.001
≥8	3.13 (1.84–5.23)	<0.001	2.71 (1.55–4.74)	<0.001	2.65 (1.55–4.54)	<0.001
Pre-RT PSA, ng/ml	3.08 (0.73–13.03)	0.1	4.86 (1.08–22.10)	0.04	5.09 (1.16–22.41)	0.03
Time from surgery to eSRT, mo	0.99 (0.99–1.00)	0.7	1.00 (0.99–1.01)	0.8	–	–
Dose of radiotherapy, Gy	0.99 (0.92–1.06)	0.8	1.00 (0.93–1.08)	0.9	–	–

CI = confidence interval; eSRT = early salvage radiotherapy; HR = hazard ratio; PSA = prostate-specific antigen; Ref = reference; RT = radiotherapy.

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Cox regression analyses, where each of the previously mentioned predictors, as well as higher pre-RT PSA, was statistically significantly associated with BCR after eSRT (all $p \leq 0.04$).

3.4. Development and internal validation of nomogram predicting the outcome of early salvage radiotherapy

Based on the coefficients of the Cox regression model that identified independent predictors of BCR after eSRT (pathologic stage, surgical margin status, pathologic Gleason score, and pre-RT PSA; Table 2, model 2), a novel nomogram was then developed to predict 5-yr BCR after eSRT (Fig. 3a). The discrimination was 0.74 when internally validated. The nomogram was well calibrated, with a good correlation between predicted and observed BCR rates after eSRT (Fig. 3b). Finally, to put these results in a clinical context, we plotted the decision curve for BCR after eSRT. This shows that, although our model is of no value for risk of BCR <15%, our nomogram improves clinical risk prediction

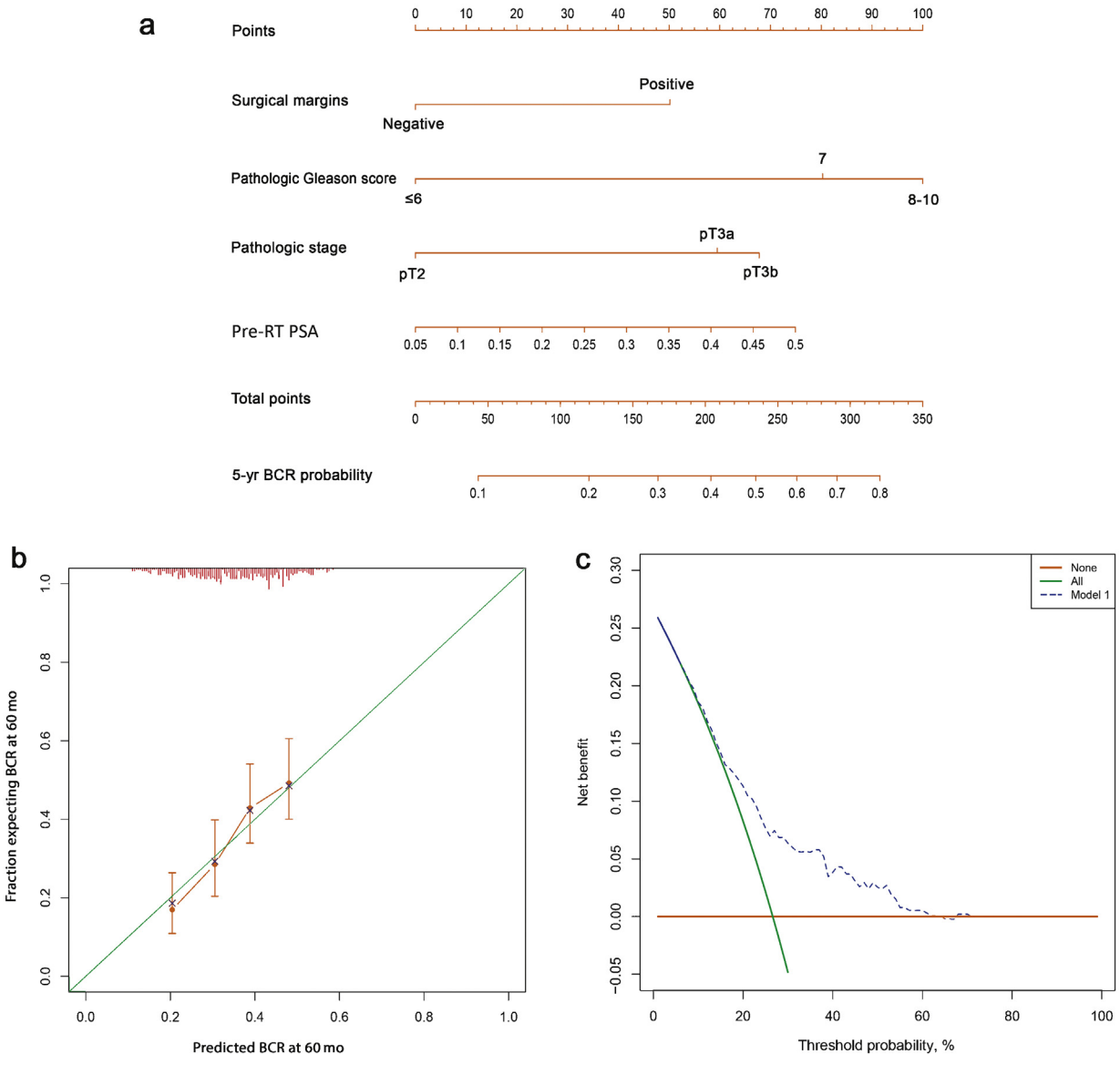

Fig. 3 – (a) Nomogram to predict the probability of biochemical recurrence (BCR) at 5 yr following early salvage radiotherapy (eSRT) for BCR after radical prostatectomy based on pathologic Gleason score, surgical margin status, and prostate-specific antigen at time of eSRT. Instructions: Locate the patient's pathologic Gleason score on the pathologic Gleason score axis. Draw a line straight upwards to the point axis to determine how many points towards the probability of BCR after eSRT the patient receives for his pathologic Gleason score. Repeat the process for each additional variable. Sum the points for each of the predictors. Locate the final sum on the total-point axis. Draw a line straight down to find the patient's probability of BCR at 5 yr after eSRT. (b) Nomogram calibration plot for nomogram predicting 5-yr BCR. Perfect predictions correspond to the 45° line. Points estimated below the 45° line correspond to nomogram overprediction, whereas points situated above the 45° line correspond to nomogram underprediction. Vertical lines indicate the frequency distribution of predicted probabilities. (c) Decision curve analyses demonstrating the net benefit associated with the use of the nomogram. Net benefit can be interpreted as the proportion of all patients who have BCR after eSRT and are recommended for additional cancer therapies if no patients without BCR were treated.
PSA = prostate-specific antigen; RT = radiotherapy.

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for men with a probability of BCR after eSRT between 20% and 60%.

4. Discussion

SRT represents the currently recommended treatment option for patients with BCR after RP and presumed or documented local failure without evidence of distant metastases [5,6]. Given the well-known association between PSA at SRT and cancer control outcomes [12,18], it is recommended that SRT be administered at the earliest sign of BCR [5,16,18]. However, even when administered early after recurrence, a certain proportion of men still experience biochemical failure [18]. Identifying these patients is crucial to optimise the use and extent of eSRT, as well as to assess the need for other concomitant systemic treatments such as androgen-deprivation therapy (ADT). Previous studies addressed the predictors of disease progression in patients undergoing SRT [7–17]. However, virtually none of them focused on patients treated exclusively with eSRT. To address this void, we sought to develop a novel nomogram to identify patients at higher risk of BCR after eSRT.

Our results have several aspects. First, we showed that eSRT is generally associated with excellent cancer control rates because roughly 75% of patients were free from recurrence 5 yr after eSRT. Although the results of ongoing randomised trials comparing adjuvant RT versus initial observation followed by eSRT in case of relapse are still awaited, such high cancer control rates seem to support the role of eSRT in the management of locally advanced/aggressive PCa.

Second, we found that tumour stage, pathologic Gleason score, and positive surgical margins represented significant predictors of BCR after eSRT. However, no differences were observed in the 5-yr BCR-free survival rates between patients with pT3a and pT3b disease. These findings suggest that, in the context of SRT administered at low PSA values, extracapsular extension or seminal vesicle invasion may have a comparable detrimental prognostic impact on the subsequent risk of cancer recurrence. However, we demonstrated that patients with non–organ-confined disease and pathologic Gleason score 8–10 had a higher risk of BCR compared with their counterparts with organ-confined or lower grade tumour. These observations highlight the likelihood of subclinical distant metastases even with low PSA levels for patients with locally advanced and/or poorly differentiated disease. Our findings corroborate observations in previous studies [9,11–13]. For example, Stephenson et al. [9] developed a nomogram to predict the probability of recurrence after SRT in a cohort of approximately 1500 patients with BCR after SRT. Similar to our results, the authors reported that Gleason score 8–10 represented an independent predictor of treatment failure. In contrast to our findings, they showed an inverse association between surgical margin status and increased risk of BCR, which other studies also confirmed [11–13]. The reason for these discrepant findings might be the stringent inclusion criteria adopted in our analyses, where all patients had undetectable PSA levels after surgery, pre-RT PSA $\leq$0.5 ng/ml, node-negative PCa, and no neo- or adjuvant treatments. Inclusion of patients with more aggressive tumour characteristics (and higher pre-RT PSA levels) might result in higher rates of undetectable micrometastases at the time of RT, thus potentially changing the prognostic significance of surgical margin status.

Third, our analyses confirmed that pre-RT PSA is a significant predictor of BCR, even in the early salvage setting. Accordingly, postoperative PSA should be carefully monitored for patients at high risk of disease recurrence to facilitate the early detection of BCR and to allow for salvage treatment in a timely fashion. However, the optimal PSA at which to administer eSRT may depend on associated disease features such as Gleason score, pathologic stage, and surgical margin status. For example, a patient with pT2 stage, negative surgical margins, and Gleason score 6 at RP has a 9% BCR probability at 5 yr after eSRT if he is irradiated at a PSA of 0.3 ng/ml. This increases up to only 13% if eSRT is given at PSA 0.5 ng/ml. Conversely, a patient with pT3a disease, Gleason score 8–10, and positive surgical margins treated with eSRT at a PSA of 0.1 ng/ml has a 45% probability of BCR 5 yr after eSRT. This increases significantly to roughly 70% if the same patients receive eSRT at 0.5 ng/ml. Therefore, although the risk of BCR after eSRT increases linearly with increasing PSA even at lower PSA ranges, the optimal PSA trigger value for eSRT should be individualised according to the features of each patient. This is in line with what was reported by Karlin et al. [12], who recently showed significantly higher BCR-free survival rates in men treated at low PSA levels. This was particularly true for patients with Gleason score 8–10, where the BCR-free survival rates at 53 mo were 77% versus 26% when RT was initiated at relapsed PSA of $\leq$0.33 versus 0.34–1.0 ng/ml, respectively. It is thus likely that the definition of BCR and the subsequent need for early salvage treatment should be modulated according to individual PCa features at RP [24] to optimise the efficacy of eSRT.

From a clinical standpoint, the results of our study have important implications. First, our nomogram could be used to identify men who might be cured by eSRT alone, as well as those who may profit from a more extensive treatment approach. For example, in patients at higher risk of recurrence after eSRT, whole-pelvis RT might be indicated and eventually safely administered. The aim of this approach would be to improve the outcomes of SRT sterilising possible micrometastatic nodal disease. Although prospective data regarding the effectiveness of whole-pelvis RT in the management of BCR after surgery are still lacking, retrospective data showed that this treatment modality was independently associated with an improvement in BCR-free survival, particularly in patients with PSA levels $\geq$0.4 ng/ml [25].

Additionally, concomitant ADT might represent a therapeutic option for patients at higher risk of relapse after eSRT. However, controversy exists regarding its role to prevent PCa progression after SRT [7,26–28], and results from ongoing prospective trials are needed to better clarify this issue. Patients at higher risk of recurrence after eSRT might also be considered optimal candidates for clinical trials evaluating the efficacy of novel therapies.

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Finally, we should underline that patients with less aggressive disease characteristics (ie, at lower risk of BCR after eSRT) might represent individuals at lower risk of experiencing clinical progression and cancer-specific mortality [3,4]. Further predictive tools are needed to identify which patient might benefit more from eSRT in terms of metastases-free and cancer-specific–free mortality.

Despite several strengths, our study is not devoid of limitations. First, BCR was the primary end point. However, this parameter represents only a surrogate marker for cancer-specific mortality [3,4], and not all the patients who experience BCR even after postoperative RT will ultimately die from PCa [29]. Unfortunately, lack of data on more solid oncologic outcomes prevented us from using systemic progression or cancer-related mortality as end points.

Second, our study does not take into account patient comorbidity. This is important, since a non-negligible proportion of patients who experience recurrence will die from other causes rather than from PCa [29]. The need for aggressive treatment modality should therefore be individualised in terms of patient profile and life expectancy. The lack of data on PSA doubling time (PSA DT) represents another limitation of our study [30]. However, the prognostic value of PSA DT was recently questioned in men with BCR and very low PSA levels [31]. Additionally, we included in our analyses time from surgery to eSRT, which can be considered a proxy of the dynamic of PSA increase.

Our study is in part limited by the inclusion of patients treated over a relatively long time interval (1993–2009). Over time, improvements might have been achieved in diagnostic, surgical, and RT techniques. Changes have also been applied to the Gleason grading system, potentially leading to different outcomes in particular subgroups of patients. Finally, although all patients underwent eSRT, the dose chosen varied according to each treating institution based on tumour and patient characteristics and physician preferences/attitudes. With respect to this issue, it is noteworthy that in our analysis radiation dose did not emerged as an independent predictor of BCR after eSRT. A role of a moderate dose escalation was indeed postulated but in a later salvage setting [32].

Our findings may therefore raise the issue of the real need for dose escalation, with its inherent acute and late side effects, in patients with extremely limited tumour burden. Nevertheless, it should also be emphasised that our analysis pertained to a cohort of patients treated at a narrow range of eSRT doses (IQR: 66.6–70.2 Gy), thus possibly leading to an underestimation of the real impact of dose escalation in this setting. We should underline that only a small number of patients included in our cohort had a 5-yr BCR predicted probability >50%. Consequently, the performance of our prediction tool might not be ideal for patients at very high risk of BCR after eSRT. Last, external validation of our nomogram is needed.

5. Conclusions

eSRT affords excellent cancer control for patients with BCR after surgery. We developed the first nomogram predicting BCR for patients receiving eSRT. Our predictive tool might thereby assist clinicians to identify the best candidates for eSRT and allow selection of patients at high risk of disease recurrence after eSRT to be considered for additional forms of therapy.

Author contributions: Alberto Briganti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Briganti, Karnes, Joniau, Boorjian, Cozzarini, Gandaglia, Shariat, Sun, Karakiewicz, Hinkelbein, Haustermans, Tombal, Montorsi, Van Poppel, Wiegel.
Acquisition of data: Briganti, Gandaglia, Boorjian, Hinkelbein, Haustermans, Tombal, Cozzarini, Wiegel.
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Appendix A. Supplementary data

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