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

*Alberto Briganti*[a,*,†], *R. Jeffrey Karnes*[b,†], *Steven Joniau*[c], *Stephen A. Boorjian*[b], *Cesare Cozzarini*[d], *Giorgio Gandaglia*[a,e], *Wolfgang Hinkelbein*[f], *Karin Haustermans*[g], *Bertrand Tombal*[h], *Shahrokh Shariat*[i], *Maxine Sun*[e], *Pierre I. Karakiewicz*[e], *Francesco Montorsi*[a], *Hein Van Poppel*[c], *Thomas Wiegel*[j]

[a] *Department of Urology, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy;* [b] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [c] *University Hospitals Leuven, Department of Urology, Leuven, Belgium;* [d] *Department of Radiotherapy, San Raffaele Scientific Institute, Milan, Italy;* [e] *Cancer Prognostics and Health Outcomes Unit, University of Montreal, Montreal, Canada;* [f] *Department of Radiation Oncology, Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany;* [g] *University Hospitals Leuven, Department of Radiotherapy, Leuven, Belgium;* [h] *Department of Urology, Université Catholique de Louvain, Brussels, Belgium;* [i] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [j] *Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany*

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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.



† Denotes equal contribution.
* Corresponding author. Department of Urology, San Raffaele Hospital, University Vita-Salute, Via Olgettina, 60, 20132 Milan, Italy. Tel. +39 02 2643 7286; Fax: +39 02 2643 7298.
E-mail address: briganti.alberto@hsr.it (A. Briganti).

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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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