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# Development and internal validation of a multivariable prediction model for biochemical failure after whole-gland salvage iodine-125 prostate brachytherapy for recurrent prostate cancer

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**ABSTRACT**

**BACKGROUND:** Localized recurrent prostate cancer after primary radiotherapy can be curatively treated using salvage iodine-125 ($^{125}$I) brachytherapy. Selection is hampered by a lack of predictive factors for cancer control. This study aims to develop and internally validate a prognostic model for biochemical failure (BF) after salvage $^{125}$I brachytherapy.

**METHODS AND MATERIALS:** Whole-gland salvage $^{125}$I brachytherapy patients were treated between 1993 and 2010 in two radiotherapy centers in the Netherlands. Multivariable Cox regression was performed to assess the predictive value of clinical parameters related to BF (Phoenix-definition [prostate-specific antigen [PSA]-nadir + 2.0 ng/mL]). Missing data were handled by multiple imputation. The model's discriminatory ability was assessed with Harrell's C-statistic. Internal validation was performed using bootstrap resampling (2000 data sets). Goodness-of-fit was evaluated with calibration plots. All analyses were performed using the recently published TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement.

**RESULTS:** After median followup of 74 months (range 5−138), 43 of a total 62 patients developed BF. In multivariable analysis, disease-free survival interval (DFSI) after primary therapy and pre-salvage prostate-specific antigen doubling time (PSADT) were predictors of BF: corrected hazard ratio (HR) 0.99 (95% confidence interval 0.97−0.999; $p = 0.04$) and 0.94 (95% confidence interval 0.89−0.99; $p = 0.03$), both for a 1-month increase (optimism-adjusted C-statistic 0.70). Calibration was accurate up to 36 months. Of patients with PSADT >30 months and DFSI >60 months, 36-month biochemical disease-free survival was >75%. Every 12-month increase in DFSI will allow 3-month decrease in PSADT while maintaining the same biochemical recurrence-free rates.

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**CONCLUSIONS:** We have presented results from a cohort of patients undergoing salvage $^{125}$I-brachytherapy. Our data show that better selection of patients is possible with the DFSI and PSADT. 

*Keywords:* Whole-gland salvage; Prostate cancer; $^{125}$I brachytherapy; Prediction model; Biochemical failure

## Introduction

Radiotherapy is an effective treatment modality for prostate cancer. Both brachytherapy and external beam radiotherapy (EBRT) show favorable outcomes in terms of biochemical control and (prostate cancer specific) survival (1−3). However, a subset of patients develops recurrent disease that is often confined to the prostate (4). The recurrence risk depends mainly on primary radiotherapy dose, Gleason grade, T-stage, prostate-specific antigen (PSA) value, and the use of androgen deprivation therapy (ADT) (3). High-risk groups can have a 10-year biochemical recurrence risk of 30−50% (2, 3).

Salvage brachytherapy (low-dose rate [LDR] or high-dose rate [HDR]) is a curative option for prostate-confined recurrences in case of biochemical failure (BF). Whole-gland salvage brachytherapy can lead to long-term biochemical control and postpone ADT use (5). Patients are eligible for salvage if they have a prostate-confined recurrence with no evidence of lymph node or distant metastases. Factors used for patient selection are T-stage, Gleason score, an interval to failure >3 years, PSA (ideally <10 ng/mL), and PSA doubling time (PSADT, ideally >12 months) (6−8). The use of other PSA metrics, such as PSA density and PSA velocity (ideally <2.0 ng/mL/y), has also been described (6, 7, 9). However, factors associated with BF after salvage brachytherapy have not been well defined in the current literature because they are based on small studies with limited events (10, 11). A few series have suggested the PSA nadir after primary therapy, pre-salvage PSA and PSADT, time to relapse after primary therapy, and primary Gleason score as possible predictors of BF using multivariable models (10−14). However, these factors vary in predictive ability among studies and are not systematically confirmed. Therefore, the aim was to develop and internally validate a prediction model for BF after salvage $^{125}$I brachytherapy. Ultimately, better patient selection could lead to the greater adoption of potentially curative salvage brachytherapy in the future.

## Methods and materials

### *Patient selection*

Permission for data analysis was obtained from the institutional review board of the University Medical Center Utrecht (UMCU), and the informed consent requirement was waived for this study. Sixty-two whole-gland salvage $^{125}$I brachytherapy patients were treated between November 1993 and April 2010 in the UMCU ($n$ = 33) and the Radiotherapeutic Institute RISO, Deventer, The Netherlands ($n$ = 29). Patients were selected for treatment based on indicators of localized recurrence. All patients with BF according to the Phoenix definition (defined as PSA nadir + 2 ng/mL) underwent transrectal prostate biopsy confirmation and assessment of metastatic disease with CT or MRI and technetium-99m scintigraphy. Patients with T3 disease were excluded based on digital rectal examination, transrectal ultrasound or, in a subset of patients, MRI ($n$ = 22). For other factors, such as age, PSA, and comorbidities, no specific guidelines were available, and the decision was made at the discretion of the treating physician (neoadjuvant). ADT or ADT used for cytoreduction was discontinued at the time of salvage.

The prescribed volume of the prostate receiving 100% or 145 Gy ($V_{100}$) was ≥95% and the minimal dose received by 90% of the prostate ($D_{90}$) ≥145 Gy. At the UMCU, treatment plans were generated with the Sonographic Planning of Oncology Treatment System (Nucletron BV, Veenendaal, The Netherlands). Planning for RISO patients was performed with Variseed (Varian Medical Systems, Palo Alto, CA). Both loose and stranded seeds were used.

### *Factors analyzed*

Clinical factors included before primary therapy were treatment type ($^{125}$I brachytherapy or EBRT), EBRT dose (dichotomized into >64.4 and ≤64.4 Gy), initial PSA, T-stage, differentiation grade (Gleason scores 2−6, 7, or 8−10), and year of primary treatment. Pre-salvage factors encompassed PSA nadir after primary treatment, biochemical disease-free survival interval (DFSI), PSA, PSADT, PSA density, PSA velocity, ADT use (yes or no, regardless of ADT type), ADT duration, and year of treatment. Pre-salvage Gleason score was not included as a predictive factor because of possible misclassification due to primary radiation effects (especially in the first 24−36 months (15)). PSA kinetics (PSADT and PSA velocity) were obtained using the Memorial Sloan Kettering Cancer Center calculation tool (16). Continuous variables were not categorized in the univariable and multivariable analyses. For the Kaplan-Meier analysis, categories were allowed. PSA nadir after salvage was separately evaluated for the effect on BF.

The PSADT was only calculated if at least three measurements were available between the nadir-value and BF after primary treatment. Data on the outcome and predictors were analyzed by the primary researcher (MP) without blinding because of the objectivity of all factors under study.