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

Max Peters[1], MD; Jochem R.N. van der Voort van Zyp[1], MD, PhD; Marinus A. Moerland[1], PhD; Carel J. Hoekstra[2], MD; Sandrine van de Pol[2], MD; Hendrik Westendorp[2], MSc; Metha Maenhout[1], MD; Rob Kattevilder[2], BSc; Helena M. Verkooijen[3], MD, PhD; Peter S.N. van Rossum[1], MD; Hashim U. Ahmed[4,5], MD, PhD, FRCS (Urology); Taimur T. Shah[4-6], MD; Mark Emberton[4,5,7], BSc, MBBS, MD, FRCS (Urology); Marco van Vulpen[1], MD, PhD.

1. Department of Radiation Oncology, University Medical Center Utrecht, The Netherlands
2. Radiotherapeutic Institute RISO, Deventer, The Netherlands
3. Imaging division, University Medical Center Utrecht, The Netherlands
4. Division of Surgery and Interventional Science, University College London, UK
5. Department of Urology, UCLH NHS Foundation Trust, UK
6. Department of Urology, Whittington Hospital NHS Trust, London, UK
7. NIHR UCLH/UCL Comprehensive Biomedical Research Centre, London, UK

Correspondence:

University Medical Center Utrecht

Department of Radiotherapy, HP. Q00.118

Heidelberglaan 100, 3584CX Utrecht, The Netherlands

Phone: 0031-88-7558800, Fax: +31-88-7555850

Email: M.Peters-10@umcutrecht.nl

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Summary

Whole-gland salvage Iodine-125-brachytherapy can postpone the need for androgen deprivation therapy. The PSA-doubling time (PSADT) before salvage and the disease-free survival interval (DFSI) after primary therapy can be used for selection. The PSADT should ideally be >30 months and the DFSI >60 months to obtain >70% biochemical disease free survival up to three years. Every 12 months increase in DFSI will allow 3 months decrease in PSADT to achieve the same recurrence free rate.

I-125: Iodine-125
BF: Biochemical failure
TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
DFSI: Disease free survival interval
PSADT: Prostate specific antigen doubling time
PSA: Prostate specific antigen
HR: Hazard ratio
EBRT: External beam radiotherapy
ADT: Androgen deprivation therapy
LDR: Low dose rate
HDR: High dose rate
DRE: Digital rectal examination
MRI: Magnetic resonance imaging
CT: Computed tomography
Gy: Gray
V…%: Volume receiving …% of the prescribed dose (145 Gy)
D…%: Minimal dose received by …% of the structure
iPSA: initial PSA
bDFS: Biochemical disease free survival
SD: Standard deviation
CI: Confidence interval

Abstract

Background: Localized recurrent prostate cancer after primary radiotherapy can be curatively treated using salvage Iodine-125 (I-125) 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 I-125-brachytherapy.

Materials and methods: Whole-gland salvage I-125-brachytherapy patients were treated between 1993-2010 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 [PSA-nadir + 2.0 ng/ml]). Missing data was handled by multiple imputation. The model's discriminatory ability was assessed with Harrell's C-statistic. Internal validation was performed using bootstrap resampling (2000 datasets). Goodness-of-fit was evaluated with calibration plots. All analyses were performed using the recently published TRIPOD statement.

Results: After median follow-up 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 [CI]: 0.97-0.999 [p=0.04]) and 0.94 (95%CI 0.89-0.99 [p=0.03]), both for a one 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.

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

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 which is often confined to the prostate[4]. The recurrence risk depends mainly upon primary radiotherapy dose, Gleason grade, T-stage, 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-metric, such as PSA-density and PSA-velocity (ideally <2.0 ng/ml/year) 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 I-125-brachytherapy. Ultimately, better patient selection could lead to the greater adoption of potentially curative salvage brachytherapy in the future.

Materials and Methods

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 I-125-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 biochemical failure according to the Phoenix-definition (defined as PSA nadir+2ng/ml) underwent trans-rectal prostate biopsy confirmation and assessment of metastatic disease with CT or MRI and technetium-99m scintigraphy. Patients with T3 disease were excluded based on either digital rectal examination (DRE), 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 (V100) was ≥95% and the minimal dose received by 90% of the prostate (D90) ≥145 Gy. At the UMCU, treatment plans were generated with the Sonographic Planning of Oncology Treatment system (SPOT, 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 (I-125-brachytherapy or EBRT), EBRT dose (dichotomized into >64.4 Gy and ≤64.4 Gy), initial PSA (iPSA), T-stage, differentiation grade (Gleason 2-6, Gleason 7, or Gleason 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 by using the Memorial Sloan Kettering Cancer Center calculation tool[16]. Continuous variables were not categorized in the uni- and multivariable analysis. 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, due to the objectivity of all factors under study.

Toxicity

Severe (≥ grade 3) late (> 6 months post-implantation) gastrointestinal (GI) and genitourinary (GU) toxicity was assessed using the common terminology criteria for adverse events (CTCAE) version 4.

Statistical analysis

Normally distributed variables are presented as mean (±SD) and variables with a skewed distribution as medians with ranges. Categorical data is presented as frequencies with percentages. Kaplan-Meier analysis was performed to assess biochemical disease-free survival (bDFS) and differences between dichotomized predictors were evaluated using the log-rank test. Categories were created based on generally accepted cutoff points (e.g. PSA ≤10 and >10 ng/ml). ROC-analysis was performed for PSA-density and PSA-velocity to identify ideal cutoff values with maximal sensitivity and specificity (equal weight), because literature cutoff points provided unbalanced groups. Patients were censored in case of death or when lost to follow-up before reaching the endpoint (BF).
Missing data was considered at random and handled using multiple imputation with the iterative Markov chain Monte Carlo method (20 iterations)[17]. Predictor variables included in the procedure were initial PSA-value, age, initial tumor grade, PSA-nadir after primary therapy, interval to nadir, DFSI, pre-salvage PSA, PSADT, PSA-density and PSA-velocity, nadir after salvage and interval to nadir. The outcome (BF) was also included[17,18].

Model development

A Cox-proportional hazards regression model was fitted, providing hazard ratios (HRs) with 95% confidence intervals (CI's). Correlation coefficients were calculated to assess collinearity among PSA, PSA-kinetic factors and other predictors. Pearson's correlation coefficient was used for linear correlations and Spearman's ρ for non-linear correlations. In case the correlation coefficient was ≥0.75, the easiest measurable factor was included. Factors were included in the multivariable analysis if $p<0.10$ based on the Wald test. Stepwise backward elimination of the least significant predictors for BF was performed. Models were compared with the likelihood ratio test statistic. The proportionality assumption of the cumulative hazard functions was assessed using log-log curves for categorical variables and Schoenfeld residuals for continuous variables. No interactions were assessed. The survival proportion formula: $S(t)=S(0)^{\exp(\beta_{predictor1}*predictor1 + \beta_{predictor2}*predictor2\ etc.)}$, was used to calculate bDFS for different levels of predictor variables from multivariable analysis[19]. The baseline survival proportion S(0) is the survival at a certain time point for patients with the determinants from multivariable analysis equaling 0. The β's are the natural logarithm of the HR's, corrected for optimism after internal validation of the model. Harrell's C-statistic was used to assess the model's discriminative ability[20]. For internal validation of the model, bootstrapping with 2000 resamples for each of the 20 imputed datasets was performed to calculate the optimism of the model, after which the C-statistic was adjusted and a shrinkage factor calculated to correct the coefficients (β's). The predictive accuracy of the final (optimism-corrected) model was visualized with calibration plots at 2, 3, 4 and 5 years. No external validation was possible.

Kaplan-Meier analysis, multiple imputation and Cox-regression procedures were performed using IBM SPSS 20.0 (SPSS Inc, Chicago, IL). R language environment (version 3.1.2) for statistical computing (available at http://www.r-project.org/[21]) was used for calibration and internal validation (survival and rms package). Statistical significance was set at $p \leq 0.05$. All analyses and reporting were performed in accordance with the recent TRIPOD statement for multivariable prediction models (www.tripod-statement.org)[22].

Results

Baseline characteristics, BF and toxicity

Mean age at salvage was 69 years (±5.3) (Table 1). Half of the EBRT patients were treated with a 64.4 Gy three-field schedule in 28 fractions of 2.3 Gy.

After median follow-up of 74 (range 5-138) months after salvage, 43 patients (69%) experienced BF. The estimated 3 and 5-year bDFS were approximately 46% and 28%. Median bDFS time was 32 months (95% CI: 17-47). Patients with a pre-salvage PSA ≤10 ng/ml had a 40% 5-year bDFS compared to 13% for patients with PSA >10 ng/ml (log rank: $p<0.001$) (Figure 1). Patients with a PSADT>10 months had a 44% 5-year bDFS compared to 5% with PSADT≤10 months ($p<0.0001$). A higher DFSI, PSA-density, PSA-velocity, and nadir after salvage also significantly increased bDFS (Table 2). Characteristics before primary radiation treatment were not associated with bDFS.

Late GI toxicity was available for 60 patients and late GU toxicity for 61 patients. A total of 12 patients (20%) were treated for radiation proctitis with argon plasma laser coagulation. Furthermore, 18 patients (30%) experienced late ≥grade 3 GU toxicity, consisting mostly of urethral strictures (n=10) and urinary retention (n=4). Lastly, 5 patients (8%) experienced a combination of severe late GU and GI toxicity, which involved two grade 3 and one grade 4 rectovesical fistula and two grade 3 rectourethral fistulas.

Missing data

No outcome data was missing. Most missing data was for PSA-velocity and DFSI (n=11, 17.7%). There was frequent overlap between missing values (≈80% of cases were without missing values). Other variables had missing data in 1.6-12.9% of cases (Table 1). Data requiring multiple measurements (e.g. PSA-velocity and PSADT) or strict (not standardized) follow-up (e.g. DFSI) was predominantly missing. Therefore, no inherent relation of missing data with the values of these parameters or with the outcome was assumed (i.e. missing at random).

Correlation

Pre-salvage PSA and PSA-density were highly correlated (Pearson's correlation coefficient 0.95 ($p<10^{-29}$)) and pre-salvage PSA and PSA-velocity (Spearman's ρ 0.80 ($p<10^{-11}$)). PSA-density and PSA-velocity were therefore excluded from multivariable Cox-regression. Other factors were also significantly correlated, but with correlations <0.75. The largest was between pre-salvage PSA and DFSI (Spearman: -0.65, $p<10^{-6}$) and DFSI and PSADT (Pearson: 0.58, $p<10^{-4}$).

Cox-proportional hazards model

After multivariable analysis DFSI and PSADT remained predictors of BF: optimism-corrected HR's 0.99 (95% CI: 0.97-0.999 [p=0.04]) and 0.94 (95%-CI 0.89-0.99 [p=0.03]), respectively (Table 3). This indicates an approximate 1% and 6% decrease in hazard for BF with every month increase in DFSI and PSADT, respectively. The discriminative ability was reasonable with an apparent C-statistic of 0.73 and 0.70 after adjustment for optimism. The shrinkage factor for the coefficients was 0.86.
PSA-density, PSA-velocity and nadir after salvage were significant predictors in univariable analyses, but were excluded due to collinearity (PSA-density and PSA-velocity) or redundancy for patients selection (PSA-nadir after salvage). Year of salvage treatment remained a significant predictor in multivariable analysis (HR: 0.91 (95%-CI 0.84-0.99 [p=0.03])) and was left in the model to correct the DFSI and PSADT.
Calibration of the model was reasonable up to 3 years (Figure 2). At 4 and 5 years, the model's predictive ability decreased. Baseline cumulative 3-year bDFS was 3%, which is the bDFS of patients with a PSADT and DFSI of 0 months. This percentage is not clinically relevant but only (statistically) necessary in calculating individual bDFS percentages based on the predictors from multivariable analysis (PSADT and DFSI). Of patients with a PSADT>30 months and DFSI>60 months, >75% remained recurrence-free until 3 years (Figure 3 and supplementary table 4). Every 12 month increase in the DFSI will allow a 3 month decrease in PSADT to obtain the same bDFS.

Discussion

A multivariable prediction model for BF in patients undergoing whole-gland salvage Iodine-125 prostate brachytherapy has been presented here. In summary our results show an estimated bDFS>75% after three years can be achieved when pre-treatment PSADT and DFSI after primary therapy are taken into account, thereby delaying the need for palliative ADT in a select group of patients. Achieving such a reasonable bDFS for patients with these characteristics might be a counter argument for the significant toxicity rates often associated with salvage therapies[5], which were also observed in this series. The model is reasonably calibrated up to 3 years, with a fairly accurate discriminative ability (C-statistic 0.70).
Interestingly, parameters prior to the primary radiation therapy showed no relation with BF after salvage brachytherapy. However, Gleason score was ≥8 in only 3 patients. With more patients, the higher primary Gleason scores could provide additional predictive power to the final model. Furthermore, changes in pathological grading might have distorted the predictive ability in this analysis.
Because of collinearity, PSA-velocity and PSA-density were excluded. These factors could possibly lead to an increased predictive ability of the model, but a simpler model was preferred. Their univariable HR's and the Kaplan-Meier analyses still give an indication of their relation with BF, which can possibly be of help in patient selection. Approximately the same is true for PSA-nadir after salvage. Although this factor is a strong predictor in univariable analysis, it is unusable for patient selection. It could however still be used to identify patients needing more strict follow-up or earlier initiation of ADT.
Our study did not assess prostate cancer-specific or overall mortality. BF remains a proxy endpoint for mortality. Even if a direct relationship between BF and mortality does not exist, appropriate patient selection based on the predictors described within this paper could delay or prevent the initiation of follow-up treatment such as ADT after BF. This would not only have a favorable influence on a patients

quality of life but also save the costs of prescribing ADT.

Previous series have described small groups of LDR salvage I-125/Pd-103 and HDR (Ir-192) patients[10-14,23,24]. Some of these studies performed multivariable Cox regression[11-14]. One study had too few events for adequate modelling[10]. Moman et al[12] assessed outcomes in 31 patients and found primary Gleason score (8-10) and PSADT to be predictors of BF. Model building and variable selection were sufficiently described, but Gleason 8-10 was only present in 2 patients, causing an imprecise HR (12.4, 95%-CI 1.9-83.2)[12]. Grado et al[11] found PSA-nadir post-salvage of <0.5 ng/ml as predictive of BF. Unfortunately, this study lacked proper description of model building, handling of missing data and variable categorization[11]. Burri et al[14] reported higher BF for patients with PSA ≥6 ng/ml (HR 8.44, 95%-CI 1.04-68.79, p=0.046). Other variables in the analysis were age (dichotomized at 70 years) and initial PSA (dichotomized at 10 ng/ml)[14]. Details regarding model building, reasons for dichotomization of variables and missing data were not provided. Henriquez et al[13] recently reported 56 salvage HDR and LDR-brachytherapy, reporting pre-salvage PSA>10 and DFSI<24 months as significantly associated with BF after Cox-regression[13]. However, proper comparison with this study is hampered by the reporting of OR's, instead of HR's. Lastly, Chen et al[10] performed univariable Cox regression in which trending data, just short of statistical significance was seen for pre-HDR salvage PSA, DFSI, number of positive cores and interval from recurrence to HDR-treatment[10]. This study analyzed the predictor variables on a continuous scale, instead of applying categorization. More recent *focal* salvage brachytherapy series, directed solely at the recurrent tumor area, have as of yet not provided any parameters associated with BF[25-27].

Thus reviewing the available literature it appears that variables after primary therapy (DFSI) and pre-salvage characteristics (PSA) may have predictive ability for BF. Our data and analysis presented in this paper adds further support for these variables. In addition, it is worth noting that data from larger series of other salvage techniques (salvage radical prostatectomy, salvage cryosurgery and high intensity focused ultrasound [HIFU]) have also shown an important role for some of these variables along with pre-salvage Gleason score in predicting BF and mortality[28-30]. Further work assessing dynamic MRI characteristics, morphology and capsular invasion of recurrent tumors may provide additional predictive ability in the future. Additionally, the improvements in staging with MRI over clinical staging can possibly allow better selection of patients for salvage treatment leading to improved oncological outcomes. It seems that more recent salvage series show improved bDFS rates, probably related to a better patient selection and treatment delivery (e.g. the adoption of HDR-brachytherapy). Thus the factors assessed in the presented analysis may not be directly applicable to the patients in these more recent salvage series[10,31].

Limitations of this study include a small sample size because of which our model precision is not optimal. This is reflected in the range of the 95%-CI's of the HR's and survival proportions. Also, the patient population is heterogeneous regarding pre-treatment characteristics and patients have been treated over a period of 17 years, possibly resulting in additional inadequacy in the predictive ability of the PSADT and DFSI. Indeed, a major limitation of this study is that year of salvage treatment remained a significant (protective) factor in multivariable analysis when combined with the DFSI and PSADT. This indicates that patient treated in a later period had a lower risk of BF, possibly due to improved or intensified selection. Therefore, it is essential to adopt a uniform selection procedure leading to a less heterogeneous patient population and more uniformity in future prediction models.

Also, whilst internal validation showed reasonable discriminative ability (adjusted C-statistic 0.70; Shrinkage factor 0.86), without external validation the predictive accuracy of the model remains preliminary; especially in the fairly heterogeneous population described here. More patients and better predictors could enhance calibration and discrimination and extend the time frame in which the model can make accurate predictions.
Regarding model building, 6 univariable significant predictors were entered in the model, for 43 events, which could lead to some destabilization of the HR's. Because of the clinical relevance of this dataset and potential predictors, the extra variables were allowed. Currently, this is the first study for salvage brachytherapy providing detailed analysis of variable selection, handling of missing data, model building, validation and calibration and outcome reporting using a standardized template for conducting and reporting in prognostic research[22]. The resulting predictors from this analysis can be used in patient selection, establishing an adequate follow-up interval after salvage I-125-brachytherapy and further prognostic research into salvage.

Conclusion

Salvage I-125-brachytherapy can provide durable biochemical control rates in adequately selected patients. The PSA doubling time before salvage and the disease-free survival interval after primary therapy were found to predict biochemical failure. Larger series and external validation of these findings in a less heterogeneous patient population are necessary.

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Figure 1: Kaplan-Meier curves depicting biochemical disease-free survival for different categories of predictor variables.

Figure 2: Calibration plots depicting the observed versus the predicted probability of biochemical disease-free survival (bDFS) at 24, 36, 48 and 60 months, respectively. The grey line is the optimal line for complete concordance between observed and predicted bDFS. On the X-axis, the distribution of predictions is depicted.

Figure 3: Biochemical disease free survival (bDFS) proportion for different categories of the predictor variables disease-free survival interval after primary therapy (DFSI) and PSA doubling time (PSADT). The 75% bDFS line is indicated.

Take home message

Whole-gland salvage Iodine-125-brachytherapy is able to provide durable biochemical control, thereby postponing the need for androgen deprivation therapy. Patients can be selected based on the PSA-doubling time before salvage and the disease-free survival interval after primary therapy.