PSA decay during salvage radiotherapy for prostate cancer as a predictor of disease outcome – 5 year follow-up of a prospective observational study

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A B S T R A C T

Background and purpose: Biochemical recurrence after prostatectomy is commonly treated with salvage radiotherapy (SRT). In this prospective observational study we investigated the PSA decay rate, determined by predefined serial PSA measurements during SRT, as a predictor for treatment outcome.

Materials and methods: Between 2013 and 2016, 214 patients were included in the study. The prescribed dose to the prostate bed was 70 Gy in 35 fractions (7 weeks) without hormonal treatment. PSA was measured weekly during SRT. Assuming first order kinetics, a PSA decay-rate constant (k) was calculated for 196 eligible patients. The ability of k to predict disease progression was compared with known clinical prediction parameters using Cox regression, logistic regression and ROC analyses. Disease progression was defined as continuously rising PSA after SRT, PSA increase by >0.2 ng/ml above nadir after SRT, hormonal treatment or clinical progression.

Results: After a median follow up of 4.7 years the estimated failure-free survival at 5 years was 56%. The PSA decay-rate constant (k) was found to be the strongest predictor of disease progression in both uni- and multivariable analyses.

Conclusion: The addition of k to established clinical variables significantly improves the possibility to predict treatment outcome after SRT and could be used to personalize future therapies.

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1. Introduction

A successful surgical treatment for localized prostate cancer (PC) should result in an undetectable prostate-specific antigen (PSA) value. Still, around 20–40% of the patients experience a biochemical recurrence (BCR) [1], usually defined as a second confirmatory PSA measurement above 0.2 ng/ml [2]. The treatment of choice for BCR is salvage radiotherapy (SRT) [3,4], commonly 66–70 Gy in 33–35 fractions to the prostate bed [5–7]. Recent evidence from randomized studies shows that the outcome can be improved with irradiation of pelvic lymph nodes [8] and hormonal therapy [9,10].

About half of the patients treated with SRT are in complete biochemical remission 3–5 years after treatment [11]. SRT failure can either occur locally (due to a target miss, radiation resistant cancer or insufficient dose), or because of nodal or distant metastases. Multiple pre-treatment clinical factors can predict outcome of SRT [1,12–17]. These predictive factors are e.g. included in a nomogram developed by Stephenson et al. [18] which calculates the probability to stay free from disease progression six years after SRT. This information can be used for selecting patients for SRT. Previous retrospective studies have shown an association between PSA change during SRT and long term outcome [19,20].

The identification of robust parameters based on each patient’s instant response to treatment, rather than using pre-treatment factors only, can be used to more effectively identify a group of patients with high risk of recurrence that are more likely to benefit from treatment escalation. This so called “enrichment” strategy is
well established in medical oncology trials to avoid dilution of treatment effects [21, 22]. Monitoring PSA change in more detail during SRT could be a potential candidate in an “enrichment” approach for this treatment. Patients who do not experience a PSA response during early SRT could for example be candidates for addition of pelvic lymph node irradiation. Whether PSA change during radiotherapy improves the predictive performance of previously recognized clinical pre-treatment parameters, as e.g. included in the nomogram described by Stephenson et al., is not well studied.

The aim of the present study was to evaluate the predictive value of PSA response during SRT and to study its impact on treatment outcome in relation to previously established prediction parameters with the long term aim to implement it in an enrichment trial set-up.

2. Materials and methods

2.1. Patients

This prospective observational study included 214 patients between February 2013 and January 2016. Men with BCR after radical prostatectomy for PC who were referred for SRT and signed a written informed consent were eligible for study inclusion. One patient withdrew his consent, twelve had either PSA0 < 0.1 ng/mL or fewer than three PSA measurements during the first five treatment weeks (making calculations of the PSA constant k not feasible) and five were excluded due to pN+ status, leaving 196 eligible patients for analysis. The definition of BCR was up to the discretion of the referring urologist. No diagnostic imaging was requested for entering the study according to Swedish national guidelines for SRT. Men with known distant metastases and/or with previous or on-going hormonal treatment were excluded. The study was approved by the Regional Ethical Review Board in Lund (reference number: 2013/2).

2.2. Salvage RT

All patients were planned for and received 70 Gy, defined as the mean dose to the planning target volume (DmeanPTV) in 35 fractions to the prostate bed. Dose specification, target volumes and organs at risk (rectum, femoral heads and urinary bladder) were defined according to recommendations by the International Commission on Radiation Units and Measurements ICRU [23–25]. Target guidelines from the RTOG were used for reference: (http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx). The Planning Target Volume (PTV) was obtained by adding a 10 mm margin to the Clinical Target Volume (CTV). Dose-volume constraints were according to local guidelines. External photon beam therapy with either 3D-Conformal Radiotherapy (3D-CRT) or Intensity-Modulated Radiotherapy (IMRT)/Volumetric Modulated Arc Therapy (VMAT) techniques was used.

2.3. PSA measurements and follow-up

PSA was measured at start of SRT (PSA0) and thereafter once weekly during the SRT course (PSA1w–7w). PSA was then recorded according to a predefined schedule at 3, 6, 12, 18 and 24 months after end of SRT, and thereafter once a year. All measurements of PSA0 and PSA1w–7w were performed at the same laboratory. Disease progression was defined as a PSA increase by ≥0.2 ng/mL above PSA nadir after SRT (or from end-of-radiotherapy in case of continuously rising PSA), initiation of hormonal treatment or clinical progression.

2.4. Statistics

The PSA change during SRT was assumed to follow a mono-exponential function with time. The PSA decay-rate constant (k) was calculated for each patient using linear regression of ln(PSA) vs. time. To test the influence of the number of PSA measurements on the estimate of k we determined it for incremental number of PSA-measurements starting with using only the first three weeks of treatment, PSA1w–3w for derivation of k1w–3w, up to all seven weeks of SRT, PSA1w–7w, yielding k1w–7w. PSA0 was not included in the calculation of k to omit the effect of a recognized transient rise in PSA commonly occurring during the first week of SRT. Progression-free survival was estimated with Kaplan-Meier analysis. To evaluate the value of k in comparison with the pre-treatment clinical variables we performed univariable and multivariable Cox regression analyses. The clinical covariates were those included in the Stephenson nomogram, i.e. PSA prior to prostatectomy (PSApre), PSA at start of SRT (PSA0), PSA doubling time (TDoubling), time between prostatectomy and SRT (TSurg-SRT), Gleason score (GS) in the prostatectomy pathology report ( dichotomized into ≤3 + 4 and ≥4 + 3), surgical margins (Surgmarg), extracapsular cancer extension (Extracaps), seminal vesicle invasion (Semves) and PSA remaining elevated (>0.1 ng/mL) after surgery (PSAelevated). Logarithmic transformations of PSA0, TDoubling and TSurg-SRT were used due to their skewed distributions. The best multivariable model was determined with the Akaike information criterion (AIC) to avoid overfitting.

| Table 1 | Baseline clinical characteristics and treatment details (n = 196). |
|---------|---------------------------------------------------------------|
| PSA prior to prostatectomy, PSApre (ng/mL) | Median (IQR) 8.5 (5.8–14.0) |
| PSA at start of SRT, PSA0 (ng/mL) | Median (IQR) 0.23 (0.16–0.37) |
| PSA doubling time post op, TDoubling (months) (n = 186)* | Median (IQR) 8 (5–17) |
| Time between surgery and SRT, TSurg-SRT (months) | Median (IQR) 33 (15–59) |
| Gleason score in prostatectomy specimen, GS | ≤3 + 4: 102 (52%) |
| | ≥4 + 3: 94 (48%) |
| Surgical margins, Surgmarg | Negative: 102 (52%) |
| | Positive: 94 (48%) |
| pT stage | T2: 90 (46%) |
| | T3a: 74 (38%) |
| | T3b: 32 (16%) |
| Extracapsular extension, Extracaps | No: 90 (46%) |
| | Yes: 106 (54%) |
| Seminal vesicle invasion, Semves | No: 164 (84%) |
| | Yes: 32 (16%) |
| pN stage, N | N0: 196 (100%) |
| | N1: 0 (0%) |
| PSA remains elevated (>0.1) after surgery, PSAelevated | No: 162 (83%) |
| | Yes: 34 (17%) |
| PSA decay constant during SRT, k1w–7w (5wks⁻¹) | Median (IQR) 0.473 (0.055–0.961) |
In addition, uni- and multivariable logistic regression analyses of disease progression within three years (the minimum follow-up time) were done with the same set of covariates. The multivariable logistic regression analyses were performed with and without \( k \) to estimate its impact in predicting disease progression and the best models were selected as described above for the Cox regression. The area (AUC) under the receiver operating characteristics (ROC) curve was also used to illustrate the predictive value of \( k \). DeLong’s test for two correlated ROC curves were used for analysing the difference between their AUCs.

Further, we ordered data by increasing \( k \) and subsequently grouped them into quartiles. The observed outcome in each ‘‘\( k \)-group’’ was then compared with the outcome calculated by the Stephenson nomogram using the web form on [https://www.mskcc.org/nomograms/prostate/salvage_radiation_therapy](https://www.mskcc.org/nomograms/prostate/salvage_radiation_therapy)

Statistical calculations were carried out using the R software ([R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org](https://www.R-project.org)). P-values < 0.05 were considered statistically significant.

### 3. Results

Clinical baseline characteristics are presented in Table 1. The median follow-up time from end of SRT was 4.7 years (IQR 4.2–5.4). The number of progression-free patients during the complete follow-up period was 111 (57%). The Kaplan-Meier estimated failure-free survival at 5 years was 56% (95% CI 49–64) as presented in Fig. 1a.

There was a strong positive correlation between \( T_{\text{doubling}} \) and \( T_{\text{surg-SRT}} \) (Spearman’s \( \rho = 0.66, p < 0.0001 \)). To avoid problems with co-linearity and the fact that the former could not be calculated for ten patients, \( T_{\text{doubling}} \) was excluded in the search for the best multivariable models.

Cox and logistic regressions were performed with \( k \) based on calculations for all time intervals (\( \text{PSA}_{1\text{w}-3\text{w}} \) to \( \text{PSA}_{1\text{w}-7\text{w}} \)). The best multivariable models (based on the AIC) were obtained for \( k \) estimated from \( \text{PSA}_{1\text{w}-5\text{w}} \), i.e. \( k_{1\text{w}-5\text{w}} \). The numerical results presented are therefore calculated with \( k_{1\text{w}-5\text{w}} \) for illustration of the model performance. As shown in Table 2, \( k_{1\text{w}-5\text{w}} \) is by far the strongest predictor of disease progression in the univariable analyses as reflected in the likelihood ratio test (i.e. the difference in –2 log likelihood between the null model and the full model). This is true independently of the time interval used for calculations of \( k \) (\( k_{1\text{w}-3\text{w}} \) to \( k_{1\text{w}-7\text{w}} \)). The second strongest predictor is \( \text{PSA}_0 \). There was only a small, not statistically significant, correlation between \( k_{1\text{w}-5\text{w}} \) and \( \text{PSA}_0 \) (\( \rho = 0.13, p = 0.08 \)).

The impact of \( k_{1\text{w}-5\text{w}} \) as a strong predictor for disease progression remained in the multivariable calculations (Table 2). This is

![Fig. 1. Progression-free survival for a) the entire patient cohort; b) the cohort divided in \( k_{1\text{w}-5\text{w}} \) quartiles; c) the cohort divided in two groups at cut-off level \( k_{1\text{w}-5\text{w}} = 0.175 \) (5 weeks \(^{-1}\)) corresponding to a specificity of 85% (sensitivity 61%), and d) at \( k_{1\text{w}-5\text{w}} = 0.600 \) (5 weeks \(^{-1}\)) corresponding to a sensitivity of 85% (specificity 62%), where the sensitivity/specificity values are from the ROC analysis of \( k_{1\text{w}-5\text{w}} \) alone according to Fig. 2.](https://www.mskcc.org/nomograms/prostate/salvage_radiation_therapy)
also demonstrated in the ROC analyses as depicted in Fig. 2. The AUC for only $k_{1w–5w}$ in the model is similar to the AUC for the multivariable model including the clinical pre-treatment variables, AUC = 0.815 and AUC = 0.812. However, the AUC for the multivariable model including all clinical pre-treatment variables and $k_{1w–5w}$ (AUC = 0.890) is significantly larger than both the former, $p = 0.002$ and $p = 0.001$, respectively. Corresponding results for $k_{1w–3w}$, $k_{1w–4w}$, $k_{1w–6w}$ and $k_{1w–7w}$ are illustrated in supplementary Fig. 1 for $k$ only and in supplementary Fig. 2 for the full model including the clinical variables. Similar area under the ROC curve values were obtained for the models determined for different $k$ intervals exceeding three weeks ($k_{1w–4w}$–$k_{1w–7w}$) while the model with $k_{1w–3w}$ did significantly worse.

Fig. 3 shows the results from the analysis with $k_{1w–5w}$ grouped in quartiles. With increasing $k_{1w–5w}$ a clear difference is seen in the observed number of patients free from disease at three years as compared with the estimated number of progression-free patients at six years using the Stephenson nomogram (https://www.mskcc.org/nomograms/prostate/salvage_radiation_therapy).

### 4. Discussion

The present prospective clinical observational trial showed that the PSA response during SRT, expressed as the PSA decay constant ($k$), is strongly predictive of treatment outcome. When tested in conjunction with the variables of the Stephenson nomogram, the PSA decay–rate constant ($k$) was found to be the strongest individual predictive factor for disease progression. The proficiency of the prediction power of $k$ is reflected by the statistically significant increase in area under the ROC curve when included in addition to the clinical variables.
to the other clinical variables from the nomogram (Fig. 2). This is further demonstrated in the graph with the number of patients without disease progression for sorted k intervals as compared to expected according to the nomogram (Fig. 3).

This is to our knowledge the first prospective trial reporting on the association between PSA decay during radiotherapy and treatment outcome. The relationship between early PSA change and treatment outcome has previously been indicated in retrospective studies [19,20]. These studies demonstrated that the quotient between PSA levels at fifth week of SRT (PSA5w/PSA0 < 1) predicts failure-free survival [19] and a drop of at least 0.2 ng/ml in PSA value at any time during SRT was associated with decreased likelihood of disease progression [20]. The PSA quotient at fifth week of SRT did also correlate to treatment outcome in our study although with a significantly inferior AUC as compared to k1w–5w (data not shown). The prospective nature of our investigation, with repeated PSA measurements at predefined time intervals, therefore makes our results a powerful addition to existing evidence.

Detailed information on the PSA decay early during treatment as presented in this study could be used for treatment monitoring and optimization. Recent randomized trials have shown significantly improved outcome by adding hormonal and pelvic lymph node treatment to SRT [8–10]. These treatment modalities are, however, associated with side effects affecting quality of life. PSA response early during SRT may be used to personalize the treatment approach by identifying those patients that are highly likely to be cured with SRT only already during treatment and sparing them from these additional treatments. By using this enrichment approach, nodal irradiation and/or hormonal therapy could be initiated selectively during SRT for non-responders, instead of upfront for all patients, to maximize treatment efficiency. Our results gave the best model for k1w–5w but as shown in supplementary Figs. 1 and 2 other PSA measurement intervals exceeding three weeks (k1w–4w–k1w–7w) could work similarly to guide treatment decisions.

No diagnostic imaging was requested for study inclusion. This was in line with Swedish national guidelines for SRT. The introduction of new imaging modalities has occurred rapidly since, with prostate-specific membrane antigen – positron emission tomography – computed tomography (PSMA-PET-CT) being one of the most promising examples. In a recent review, PSMA-PET demonstrated detection rates as high as around 33% and 45% for baseline PSA intervals of 0.0–0.19 ng/ml and 0.20–0.49 ng/ml, respectively [26]. Other studies have shown that PSMA-PET has the potential to affect treatment decision in up to almost one third of the cases [27]. This is however most often not confirmed histologically and further studies are needed to outline the true diagnostic accuracy and clinical benefit of PSMA-PET at low PSA levels. Our proposed method of predicting outcome with PSA response can be used in combination with novel imaging methods to support the accuracy of the diagnostic findings made prior to SRT as well as guiding treatment for patients without radiological findings.

There are a number limitations to our work. The results are based on a relatively small number of patients from a single centre study and the results have to be confirmed in future prospective clinical trials. However the results presented here are based on an unselected consecutively included patient cohort from a prospective, ethics review board approved clinical trial with a predefined treatment and analysis schedule which limits the risk of bias.

5. Conclusions

In conclusion, we found that the PSA decay–rate constant (k) is the single strongest predictive factor for disease progression after prostate cancer SRT. k significantly improves the possibility to predict treatment outcome which could be used to personalize SRT. Longer term follow-up and verification in future trials is needed to confirm our observations. We are already testing this concept in a prospective phase II trial to validate our results, where we in combination with advanced imaging methods select patients for enhanced treatment based on PSA response during SRT (PROPER (NCT02699424) – started inclusion early 2016).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.05.008.

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