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ORIGINAL ARTICLE

Parameters derived from the postoperative decline in ultrasensitive PSA improve the prediction of radical prostatectomy outcome

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Abstract
Purpose Contemporary tools estimating increased risk of prostate cancer (PCa) relapse after radical prostatectomy (RP) are far from perfect and there has been an intensive search for additional predictive variables. We aimed to explore whether the parameters of postoperative ultrasensitive prostate-specific antigen (PSA) decline provide additional information for predicting PCa progression.
Methods A total of 319 consecutive men, with at least 2 years of follow-up after RP for clinically localized PCa were subjected to this study. Intensive postoperative measurements of ultrasensitive PSA resulted in total of 4028 PSA values available for statistical evaluation. Biochemical recurrence (BCR) was defined as PSA $\geq$0.2 ng/ml. The accuracy of predictive models was quantified with the area under the curve.
Results Over a median follow-up of 43 months (24–99 months), 107 patients (34 %) experienced BCR after RP. In patients with BCR, significantly higher values of PSA nadir ($p < 0.001$) and a decreased time interval from surgery to reach PSA nadir ($p < 0.001$) were observed. A multivariable Cox regression model confirmed that PSA nadir >0.01 ng/ml (HR 6.01, 95 % CI: 3.89–9.52) and time to PSA nadir <3 months (HR 2.86, 95 % CI: 1.74–5.01) were independent predictors of BCR. The inclusion of PSA nadir and the time to PSA nadir into the model resulted in improvement of predictive accuracy by 16 % over the model designed on the basis of established parameters.
Conclusions Our results demonstrate that the level of PSA nadir and the time to PSA nadir determined by ultrasensitive assay significantly improve the identification of patients who are at high risk of disease recurrence after RP.

Keywords Prostate cancer · Prognosis · PSA · Radical prostatectomy

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Introduction

Serum prostate-specific antigen (PSA) declines to undetectable levels after radical prostatectomy (RP) for localized prostate cancer. The significant postoperative rise in the serum PSA is termed as the biochemical recurrence (BCR). Although controversy continues to surround the proper definition of BCR, it has been shown that BCR can signal cancer activity well before any clinical signs of disease recurrence [1]. Despite early detection and aggressive intervention, up to 40 % of patients are likely to experience BCR after RP at some time during their lifetime [2]. Accurate identification of patients at high risk of cancer relapse is of obvious importance, as treatment decisions are largely based on this information [3]. Several second line treatment options, including life-long hormonal therapy are suggested for patients at increased risk of cancer relapse after RP. Some of these strategies even form the basis for a new standard of care [4, 5]. However, the degree of accuracy with which we are able to identify men at high risk of cancer relapse is considerably limited.

Several studies have attempted to identify pre- and post-treatment variables that could have prognostic value with regard to the likelihood of disease progression after surgery [6]. The most widely recognized parameters include

preoperative PSA value and pathological features of the specimen after RP such as the Gleason sum, tumor staging, seminal or lymph node invasion, and surgical margin status. Numerous reports have described different predictive nomograms, multivariate analyses and artificial neural networks incorporating these conventional variables in efforts to improve patient counseling and management in daily clinical practice [7–9]. However, these predictive tools remain imperfect in their discrimination properties. Despite better understanding of the biological behavior of prostate cancer, further improvement in the accuracy of existing models is limited by the lack of additional readily available predictive variables [10, 11].

PSA kinetics has been extensively investigated for their usefulness as predictors of BCR. Although many studies have evaluated the importance of postoperative rise of PSA in terms of doubling time, little is known of postoperative PSA decline to conventionally undetectable levels [12–14]. In this study, we aimed to investigate in detail the dynamic of postoperative decrease in serum PSA with the use of ultrasensitive PSA assays in order to define potential new parameters that could improve prediction of BCR after RP.

Methods

Patient population

The study has received ethical approval by institutional review board. Data from 690 consecutive patients who underwent RP for clinically localized prostate cancer between May 2001 and February 2010 at our institution were evaluated. Of those, 467 patients had at least 2 years of postoperative follow-up data. Patients with PSA nadir greater than 0.1 ng/ml were classified as radical prostatectomy failure and were excluded from the study ($n = 119$). In accordance with the management policy of our institution, immediate secondary therapy in terms of radiation or hormonal treatment was recommended to these patients. In order to provide the most accurate calculation of postoperative PSA dynamic, patients with the evidence of hormonal therapy and/or radiotherapy prior to the surgery were excluded from the study as well ($n = 10$). Individuals with incomplete follow-up data for proper calculation of PSA nadir and time to PSA nadir ($n = 15$) were not included in the analysis. Additionally, since pelvic lymphadenectomy was not routinely performed in all of the patients, nodal involvement was not included in the statistical analysis and these patients ($n = 4$) were excluded from the study. This resulted in a final cohort of 319 patients available for statistical evaluation. Statistical comparison of clinico-pathological characteristics of patients excluded from the study did not differ significantly from the studied cohort (Chi-square test, Mann–Whitney test). Tumors were staged according to the 2002 TNM staging system. Prostate cancer Gleason grading was performed by a dedicated genitourinary pathologist [15].

Follow-up

The patients' follow-up consisted of ultrasensitive serum PSA level measurements, physical examination, and quality of life assessment at an interval of 2 weeks, 1, 2, and 3 months after surgery, and then subsequently every 3 months thereafter. All the PSA tests were performed in a single hospital laboratory under standardized settings using the Immulite third-generation PSA assay (Diagnostic Products Corp, Los Angeles, California; lower detection limit 0.003 ng/ml). PSA nadir was determined as the lowest postoperative value of PSA. To accurately evaluate the potential of PSA nadir and the time interval taken to reach PSA nadir, as a reliable predictor of BCR, only patients with PSA measurements 3 months before the PSA nadir and 3 months after this were included in the study. This was done in order to ensure that PSA nadir had been reached during that specific time interval. A total of 3659 ultrasensitive PSA measurements were evaluated in the final analysis. Changes of PSA not exceeding the analytical sensitivity of the assay (0.01 ng/ml) were noted as insignificant. Biochemical recurrence was defined as a single postnadir PSA level of 0.2 ng/ml or greater, and the recurrence date was assigned to the first PSA value $\geq$0.2 ng/ml.

Statistical methods

Statistical analysis was performed using the SAS statistical software program JMP 6 (SAS Institute, Cary, NC, USA). Mann–Whitney test and Chi-square test were used to compare several variables between groups of patients. Biochemical recurrence-free survival curves comparing different groups of patients were calculated using the Kaplan–Meier product-limit method, with significance evaluated by two-sided log-rank statistics. Patients were censored at the time of their last tumor-free clinical follow-up appointment. The cutoff values of continuous variables (preoperative PSA, PSA nadir, time to PSA nadir) that best predicted the biochemical progression were determined by using the Partition platform of the software. Pearson's correlation coefficient was used to examine the relationship between continuous variables. Multivariate analysis was performed using the Cox proportional hazard model. The receiver operating characteristic curve (ROC) and area under the curve (AUC) were determined to describe the accuracy in predicting BCR postsurgically. The significance of the difference between areas under ROC curves of different

Table 1 Clinical and pathological characteristics of the 319 patients with clinically localized prostate cancer

Characteristics	Number	Percent
Age (year, range)	63.00 (42–80)	–
Preoperative PSA (ng/ml, range)	7.44 (1.27–59.70)	–
>10 ng/ml	89	27.9
>20 ng/ml	18	5.6
PSA nadir (ng/ml)	0.009 (0.003–0.135)	
>0.01 ng/ml	114	35.7
Time to PSA nadir (months, range)	2.0 (0.5–30)	
<3 months	216	67.7
Clinical stage		
T1	192	60.2
T2	116	36.4
T3	11	3.4
Biopsy Gleason sum		
≤6	274	85.9
7	36	11.3
≥8	9	2.8
Pathological extracapsular extension	69	21.6
Pathologic Gleason sum ≥7	92	28.8
Positive surgical margin	56	17.6

Data are presented as number and percent of patients or as median value and range

predictive models was assessed using the method of DeLong et al. [16].

Results

During the median follow-up interval of 43 months (24–99 months), a total of 107 patients (34 %) experienced BCR. Table 1 lists the clinico-pathological details for the entire evaluated population. The median time to BCR was 21 months (3–90 months). Table 2 demonstrates the differences in several parameters between the groups of patients divided according to the appearance of BCR during follow-up. Regression analyses showed a significant relationship between preoperative PSA and PSA nadir ($r = 0.27$, $p < 0.001$). There was no correlation between time to PSA nadir and preoperative PSA ($r = -0.91$, $p = 0.105$) or between time to PSA nadir and PSA nadir ($r = -0.12$, $p = 0.129$). Figure 1 contains the Kaplan–Meier survival curves showing an apparent difference in the probability of BCR in patients stratified according to the value of PSA nadir and time to PSA nadir. The results of univariate and multivariate analysis of factors of possible prognostic value for BCR after radical prostatectomy are depicted in Table 3. Figure 2 shows the ROC curves of different predictive models. The AUC for the base model designed on the basis of established parameters (preoperative PSA value, pathological Gleason sum, extracapsular extension, and surgical margin status) was 0.70 (CI: 0.65–0.75). When the base predictive model was complemented with PSA nadir, the AUC increased significantly to 0.83 (CI: 0.80–0.88, $p < 0.0001$). Addition of both parameters of postoperative ultrasensitive PSA decline (PSA nadir and time to PSA nadir) resulted in further significant improvement in prediction accuracy (AUR 0.86, CI: 0.81–0.89, $p = 0.032$).

Discussion

Comparing studies on PSA kinetics after RP, some have used PSA assays with lower detection limit of 0.1 ng/ml and higher [12]. Other studies have combined PSA values from several laboratories using different assay methods [14, 17]. The calculation of the PSA nadir has been often based only on a limited amount of PSA measurements obtained during relatively long time period [13, 18]. Further, a number of authors have included patients with very short follow-up after RP [13, 19]. To overcome these limitations, we present a single institution and single laboratory study, with all the PSA measurements performed by equal PSA assay. The ultrasensitive PSA test used in the present analysis had a functional sensitivity of 0.01 ng/ml, which is in the order of magnitude greater than that of other conventional assays. A total of 4028 ultrasensitive measurements were analyzed. Only patients with a complete set of PSA measurements needed for the accurate calculation of PSA nadir were included. It has been stated that the majority of BCR (80 %) appears in the first 2 years after the operation [7]. Thus, only men with minimum follow-up of 2 years after RP were included in our study.

During the median follow-up of 43 months (range 24–99 months), a total of 107 patients (34 %) experienced BCR. The risk of BCR was strongly associated with the level of PSA decline. Multivariate models showed that patients with a postoperative PSA nadir of more than 0.01 ng/ml had an 85 % probability of experiencing BCR (HR 6.01, 95 % CI: 3.89–9.52). These results are compatible with several reports on prognostic significance of ultrasensitive PSA nadir [13, 14, 17]. Moreover, our analysis showed that those patients who reached the PSA nadir within the first 3 months after surgery had an increased risk of BCR by 186 % (HR 2.86, 95 % CI: 1.74–5.01). A possible explanation for this finding may be that the PSA level drops only as far as the baseline level of PSA being produced by residual cancer tissue in the pelvis or by occult micro-metastases already present at the time of surgery. According to this hypothesis, in patients who are fully cured after RP and have no residual cancer tissue

Table 2 Differences in potential predictive parameters between groups of patients according to the appearance of BCR

Parameters	BCR	BCR-free	*p* value
Pre-operative PSA (ng/ml, range)	8.76 (3.40–34.56)	6.93 (1.27–59.70)	<0.001
Pathologic Gleason sum ≥7	48 (44.85 %)	44 (20.75 %)	<0.001
Pathological extracapsular extension	34 (31.78 %)	35 (16.51 %)	0.002
Positive surgical margin	24 (22.42 %)	32 (15.09 %)	0.109
PSA nadir (ng/ml, range)	0.035 (0.002–0.100)	0.007 (0.002–0.053)	<0.001
Time to PSA nadir (months, range)	1.76 (0.5–30)	3.58 (0.5–30.00)	<0.001

Data are presented as number and percent of patients or as median value and range

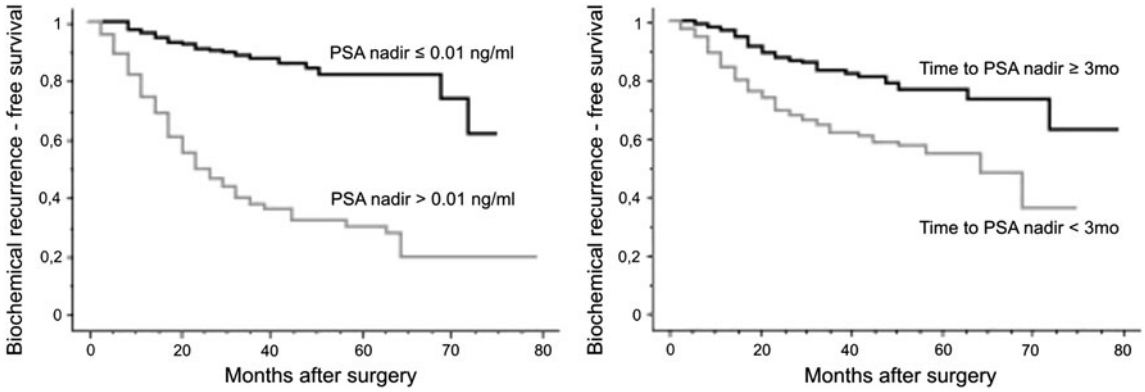

Fig. 1 Kaplan–Meier estimates of biochemical recurrence—free probability in 319 patients after radical prostatectomy stratified by the level of PSA nadir and the time to PSA nadir (Log-rank test $p < 0.001$)

producing any significant amounts of PSA, the decline of PSA measurements to the ultrasensitive PSA nadir value is longer.

The predictive accuracy of the most widely used preoperative model for the prediction of biochemical recurrence after radical prostatectomy ranges from 79 to 86 % [6, 10, 20]. The factors that predicted the outcome of RP in terms of BCR were preoperative PSA, Gleason score, lymph node status, seminal vesicle invasion, extracapsular extension, and positive surgical margin status. Same factors were tested in Cox regression analysis of our patients after radical prostatectomy. However, only extracapsular extension and a pathological Gleason score were significantly associated with the predicted outcome of surgery. Concordance index of our predicting model achieved the value of 70 %. Additional variables derived from postoperative PSA decline like PSA nadir and time to PSA nadir demonstrated a powerful ability to improve the models accuracy by 16 %.

This study has several potential limitations. These include limitations inherent to any retrospective study. Results may be influenced by selection bias. In this study group, restricted amount of patients with locally advanced prostate cancer was admitted for surgery treatment, which

Table 3 Univariate and multivariate Cox regression analyses for the prediction of biochemical recurrence after radical prostatectomy for clinically localized prostate cancer

Parameters	Cox regression			
	Univariate		Multivariate	
	Hazard ratio (95 % CI)	*p* value	Hazard ratio (95 % CI)	*p* value
PSA before surgery >10 ng/ml	2.39 (1.61–3.52)	<0.001	1.21 (0.79–1.83)	0.359
Pathologic Gleason sum ≥7	2.63 (1.77–3.88)	<0.001	1.80 (1.15–2.80)	0.009
Extracapsular extension	2.24 (1.46–3.35)	<0.001	1.68 (1.05–2.67)	0.031
Positive surgical margin	1.64 (1.00–2.56)	0.048	1.19 (0.73–1.89)	0.465
PSA nadir >0.01 ng/ml	6.93 (4.56–10.82)	<0.001	6.01 (3.89–9.52)	<0.001
Time to PSA nadir <3 mo	3.27 (1.99–5.71)	<0.001	2.86 (1.74–5.01)	<0.001

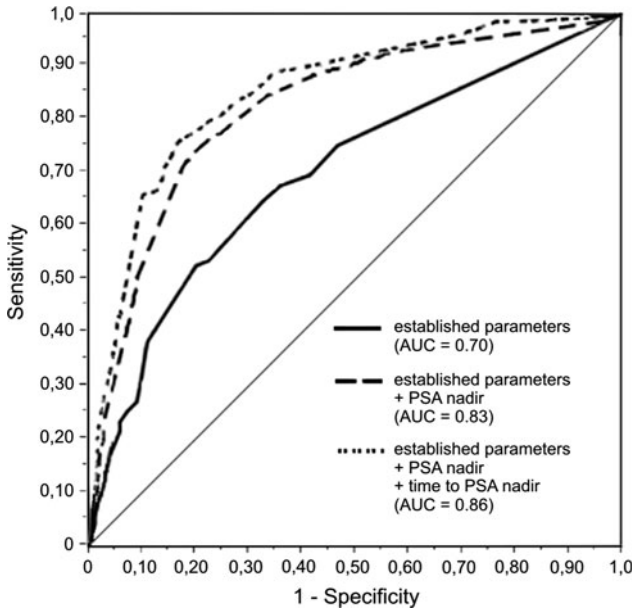

Fig. 2 Plot of ROC (receiver operating characteristics) *curves* showing predicted probabilities of biochemical recurrence on the basis of established parameters (preoperative PSA, pathological Gleason sum, extracapsular extension, and surgical margin status), established parameters plus PSA nadir and established parameters plus PSA nadir and plus time to PSA nadir

could partly explain low-risk characteristics of analyzed cohort. Thus, true external validation with an independent data set is needed to confirm the conclusions of presented paper. Another limitation is an unclear prognostic and therapeutic implication of BCR. Elevation of serum PSA value after RP can signal that prostate cancer has reappeared in some form and most experts would agree that postoperative serum PSA concentration of 0.2 ng/ml constitutes a true BCR. It has been shown that during 8 years of follow-up approximately 37 % of patients with BCR will develop clinical metastasis and 57 % of these patients will die of prostate cancer within the next 5 years [1]. However, although BCR is a surrogate end point for clinical progression, not all patients with BCR will progress to clinical relapse. Thus, the clinical usefulness of these new predictive parameters must be confirmed by their ability to add unique prognostic information with regard to prostate cancer metastases and survival.

Conclusions

Our analysis suggests that variables derived from the dynamic of postoperative PSA decline to very low levels appear to further improve the accuracy of existing predictive tools. More accurate nomograms could improve patients' selection and identification of high-risk individuals, thus allowing for better judgments about postoperative surveillance strategy and the need for secondary therapy.

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Conflict of interest There is no conflict of interest.

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