Complexed prostate-specific antigen for the diagnosis of biochemical recurrence after radical prostatectomy

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OBJECTIVES

To determine the validity of using complexed prostate-specific antigen (cPSA) levels for diagnosing biochemical recurrence after radical prostatectomy (RP).

RESULTS

In the regression models, tPSA and cPSA were highly correlated ($r = 0.99$). For the diagnosis of biochemical recurrence, tPSA thresholds of 0.20 and 0.40 ng/mL corresponded to cPSA thresholds of 0.12 ng/mL (95% confidence interval 0.08–0.17) and 0.29 (0.22–0.28) ng/mL, respectively. For the detection of biochemical recurrence, a cPSA threshold of 0.12 ng/mL had a sensitivity of 96%, specificity of 88%, positive predictive value of 89%, negative predictive value of 88%, positive likelihood ratio of 8, and negative likelihood ratio of 0.05; the respective values for a cPSA threshold of 0.29 ng/mL were 96%, 96%, 96%, 96%, 24 and 0.04.

CONCLUSIONS

cPSA has high validity for the diagnosis of biochemical recurrence after RP. Pending external validation, cPSA might be useful for biochemical surveillance after RP.

KEYWORDS

complexed prostate specific antigen, cPSA, biochemical recurrence, radical prostatectomy
recurrence. The secondary outcome was the correlation of cPSA with tPSA in monitoring patients diagnosed with biochemical recurrence.

In 50 patients, linear regression modelling was used to calculate the correlation between cPSA with tPSA levels, and to predict cPSA values corresponding to two commonly used tPSA thresholds for biochemical recurrence, i.e. 0.20 and 0.40 ng/mL [17]. In an additional 100 patients, the sensitivity, specificity, predictive values and likelihood ratios for each cPSA threshold were then determined with 2×2 table analysis (25 cases with tPSA greater than the threshold and 25 controls with tPSA less than the threshold) using each of the tPSA thresholds as the reference standard.

In 15 patients with biochemical recurrence, cPSA and tPSA concentrations in 144 serial serum samples (tPSA 0.02–47.4 ng/mL) were compared using linear regression modelling with robust variance estimates to account for multiple measures over time in the same individuals.

RESULTS

Among 50 patients with a detectable tPSA level of <1.0 ng/mL, the mean (s0, range) tPSA level was 0.58 (0.16, 0.34–0.98) ng/mL and the mean cPSA was 0.36 (0.12, 0.17–0.67) ng/mL. tPSA and cPSA correlated highly (r = 0.99, P < 0.001; Fig. 1). In the regression model, tPSA values of 0.2 and 0.4 ng/mL predicted cPSA values (95% CI) of 0.12 (0.08–0.17) and 0.29 (0.22–0.28) ng/mL, respectively.

With a predicted cPSA of 0.12 ng/mL, the mean tPSA and cPSA for the 25 controls was 0.15 (0.03, 0.08–0.19) and 0.09 (0.03, 0.03–0.19) ng/mL, respectively. The sensitivity of cPSA at a threshold of 0.29 ng/mL was equivalent to that for 0.12 ng/mL, but the specificity and predictive values were higher (Tables 1 and 2).

In 15 patients diagnosed with biochemical recurrence longitudinal estimates of cPSA and tPSA correlated highly (r > 0.99, P < 0.001; Fig. 2); this analysis included serial PSA levels in one patient with biochemical recurrence treated with androgen ablation 54 months after surgery.

DISCUSSION

In this cohort of prostate cancer patients treated with RP, cPSA levels correlated highly with tPSA levels and had high validity for the diagnosis of biochemical recurrence. These data suggest that cPSA might serve as an alternative to tPSA for biochemical surveillance after RP, and raises the possibility that cPSA might also be applicable to surveillance after primary radiotherapy, cryosurgery and androgen ablation.

In one previous analysis of patients with early- and late-stage prostate cancer, which...
included those treated with RP, there was a high concordance of serial cPSA levels with clinical status in 97% of men [18]. By contrast, in the present study we determined the validity of cPSA as a serum marker for biochemical recurrence by using tPSA as the reference standard.

These data also show, for the first time, the applicability of cPSA to a routine clinical function other than prostate cancer screening and diagnosis. The specificity of cPSA for prostate cancer detection is comparable to the combination of tPSA and free PSA [12]. Replacing several serum tests with a single PSA isof orm would probably limit confusion and redundancy while optimizing prostate cancer detection and reducing unnecessary prostate biopsies. Indeed, the potential now exists for cPSA to fulfill all of the roles currently performed by tPSA, including screening and diagnosis, prognostication in staging nomograms [19], and longitudinal monitoring of patients with prostate cancer.

Although the present validity of cPSA was generally higher at a threshold of 0.29 ng/mL (corresponding to a tPSA level of 0.40 ng/mL) than of 0.12 ng/mL (tPSA 0.20 ng/mL), the use of separate PSA ranges for analysing separate thresholds precluded direct validity comparisons between thresholds. We used different PSA ranges to restrict the analyses to clinically relevant values around each threshold (Table 2). The use of a single range would have incorporated PSA values much greater than the threshold, which would probably have increased the sensitivity for detecting biochemical recurrence. Instead, we chose a more conservative approach to maximize the potential external validity of the results.

We used several different measures to estimate the clinical validity of cPSA. The positive predictive value (the proportion of patients testing positive who actually have the disease) is a particularly useful measure, but depends in part on the prevalence of the disease in the study population; the higher the prevalence, the greater the positive predictive value [20]. The prevalence of biochemical recurrence in this selected group was 50%. As biochemical failure typically occurs in about a third of patients after RP it is possible that the positive predictive value would be less in an unselected clinical series of patients.

Another caveat on the results is that that the estimated cPSA thresholds for biochemical recurrence (0.12 and 0.29 ng/mL) are preliminary. External validation in other study populations should be done before routine use in clinical practice.

In conclusion, cPSA has high validity for detecting biochemical recurrence after RP. Pending external validation, cPSA might be useful for biochemical surveillance after RP.

CONFLICT OF INTEREST
Carol Cheli is an employee of the sponsor. Source of funding: Bayer Pharmaceutical.

REFERENCES
10 Babaian RJ, Naya Y, Cheli C, Fritsche HA. The detection and potential economic value of complexed prostate specific antigen as a first line test. J Urol 2006; 175: 897–901
11 Martin BJ, Cheli CD, Sterling K et al. Prostate specific antigen isof orms and human glandular kallikrein 2 – which offers the best screening performance in a predominantly black population? J Urol 2006; 175: 104–7
13 Sozen S, Eskicorapci S, Kupeli B et al. Complexed prostate specific antigen density is better than the other PSA derivatives for detection of prostate cancer in men with total PSA between 2.5 and 20 ng/mL: results of a prospective multicenter study. Eur Urol 2006; 47: 302–7
17 Moul JW. Variables in predicting survival based on treating 'PSA-only' relapse. Urol Oncol 2003; 21: 292–304


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Abbreviations: RP, radical prostatectomy; (c)(t)PSA, (complexed) (total) PSA.