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Prediction of tumor recurrence after radical prostatectomy using elimination kinetics of prostate-specific antigen

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Summary. The serum half-life of prostate-specific antigen (PSA) calculated subsequent to radical prostatectomy can serve to predict which patients are at high risk of bearing residual prostatic carcinoma despite their initial attainment of undetectable PSA serum levels. This report updates previous results to a mean follow-up period of 37 months. The initial results are essentially confirmed in that a mean PSA elimination half-life of 1.6 days in patients considered to be cured at least 24 months after prostatectomy provides additional useful information for predicting outcome in patients with potentially curable prostate cancer.

Many investigations have tried to correlate absolute serum PSA values with histopathological findings [10]. Most of those correlations were considered to be rather weak after long-term experience [1] unless combined with other preoperative parameters [5]. The greatest clinical usefulness of PSA lies in monitoring of patients after definitive therapy. The failure of serum PSA to reach undetectable levels after surgery is evidence of the presence of residual local disease or metastasis and, therefore, a poor prognostic indicator [2, 6–8, 11, 16, 17]. Retrospectively, in one study all of the patients whose PSA values exceeded 0.4 ng/ml after radical prostatectomy were found to have evidence of recurrence [6], whereas in another investigation, biopsy of the urethral vesicle anastomosis proved the existence of residual prostate cancer in almost half of the patients with increased PSA levels after radical prostatectomy [7]. Since local recurrence without an elevated PSA level in the absence of adjuvant treatment has not been found [7] or is rare [4], the use of serial PSA determinations for monitoring of patients after radical prostatectomy has become routine in clinical practice.

Prior to 1992 there were three investigations calculating the elimination half-life of PSA following radical prostatectomy. Regardless of the outcome of disease, half-lives of 1.9 [11], 2.2 [16], and 3.2 days [8] were reported. PSA half-life and factors regulating PSA kinetics have recently been investigated in athymic mice [3]. The PSA doubling time has been used to calculate the kinetics of cancer volume increase in untreated prostatic carcinoma [14].

Under the hypothesis that residual local or distant prostatic carcinoma is capable of producing PSA, half-life calculations should reveal a longer half-life if there is remaining tissue capable of prolonging PSA decay during the phase of elimination. Assuming that PSA production no longer occurs in disease-free patients, the half-life is expected to be short. In patients with diminished but continuing PSA production, the half-life is supposed to be longer, furnishing evidence of residual disease. In 1992 we reported a half-life study in which the differentiation was made between half-lives in patients who were considered to be cured as judged by serially undetectable PSA levels and patients who had evidence of residual tumor. With a minimal follow-up period of 10 months, we found a mean half-life of 1.54 days for cured patients, whereas patients who had recurrent PSA or failed to achieve undetectable PSA levels showed a mean half-life of 2.98 and 3.05 days, respectively [15]. We present the results we obtained after extending the mean follow-up period to 37 months, with a minimum of 24 months having elapsed after radical prostatectomy.

Patients and methods

Patient population and techniques

A total of 52 patients undergoing radical prostatectomy for adenocarcinoma of the prostate were included in a prospective investigation for PSA half-life calculation. None of the patients (age, 50–74 years; median and mean, 63 years by the time of surgery) showed evidence of distant disease in the preoperative staging evaluations. Two of the patients received hormonal therapy from their practitioner prior to surgery, which was not known by their consultant urologist nor by the authors at the time of the previous investigation. Both patients were excluded from the present evaluation because hormonal suppression of PSA pro-

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duction [9] in addition to surgical removal of the prostate might lead to an underestimation of the half-life. The remaining patients were not subjected to any anti-cancer treatment besides surgery during the follow-up period reported in this paper.

The PSA serum concentrations used for calculation of half-lives were determined with a solid-phase, two-site monoclonal immunoenzymetric assay (Tandem-E, Hybritech). The minimal concentration of serum PSA that was detectable by the assay as performed in our laboratory was 0.16 ng/ml [15], being in close concordance with a previous report investigating the radioimmunometric assay from the same producer [13]. Blood samples were drawn at 30 min prior to the operation, within 5 min after removal of the prostate specimen by radical retropubic prostatectomy (t_0), and on postoperative days 1, 2, 3, 4, 7, 14, and 21. Patients were considered to have undetectable levels if the PSA value reached ≤ 0.2 ng/ml. Following hospital discharge, the serum PSA value was determined approximately every 3 months. The follow-up to determine the interval of nondetectable serum PSA values ranged from 24 to 47 months (mean, 37 months; median, 36 months). Since some of the patients were monitored outside the hospital by polyclonal radioimmunoassays, all patients were classified as having serologically relapsed when at least two consecutive PSA serum determinations exceeded 0.9 ng/ml, regardless of the assay technique. No patient was lost to follow-up.

Statistical analysis

Nonparametric comparisons were used as previously described [15]. Half-life calculations began with the sample drawn at 5 min after removal of the prostate (t_0). Assuming an exponential model for serum PSA decay (first-order elimination kinetics) as a function of time (t), the PSA half-life was calculated for each individual patient. The model $PSA_{(t)} = PSA_{(t_0)} \times e^{(-bt)}$, where b is the elimination constant, was fitted using the least-squares technique (Gauß). Half-lives were calculated as (ln 2)/b. Statistical significance was calculated using the two-tailed Wilcoxon rank-sum test. Calculations of correlations utilized Kendall's Tau_c. All statistical variances are reported as standard deviations (SD).

Of the 52 patients who underwent serial determinations for PSA half-life, two patients were excluded because of preoperative hormonal therapy and one patient could not be evaluated because of a poorly fitting regression, leaving 49 patients for the analysis.

Results

Of the 49 patients included in serum PSA half-life calculations, the values absolute PSA of 23 remained under 0.9 ng/ml for 24–47 months of follow-up (mean, 37 months; median, 36 months). In all, 22 patients progressed serologically as reflected by a PSA elevation above 0.9 ng/ml or did not attain undetectable PSA levels defined as ≤ 0.2 ng/ml. Patients who achieved undetectable PSA levels but relapsed did so within 1–19 months (median, 7 months; mean, 8 months). The remaining 4 patients achieved undetectable PSA levels but have not yet been monitored long enough to fulfill the criterion of at least 24 months of undetectable PSA levels for classification as being potentially cured.

Our findings can be summarized as follows:

1. The mean PSA serum half-life for patients who were potentially cured by radical prostatectomy was 1.62 ± 0.68 (SD) days. The half-lives for these patients differed significantly ($P < 0.02$) from the half-lives of those who showed a serological relapse during the follow-up period (Fig. 1).

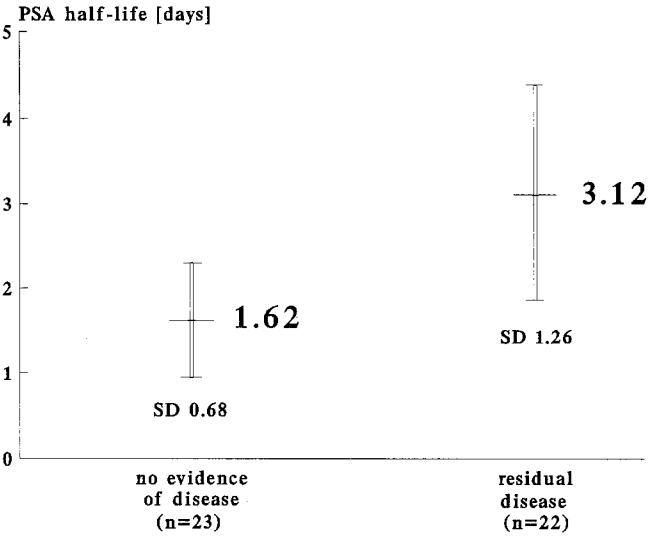

Fig. 1. PSA half-life according to disease outcome as judged by postoperative absolute PSA levels measured in the follow-up after 24–47 months

2. The mean PSA serum half-life for patients who either did not attain undetectable PSA serum levels or relapsed serologically was 3.12 ± 1.26 (SD) days (Fig. 1).
3. The mean PSA serum half-life for all patients who achieved undetectable PSA levels within 21 days, regardless of the disease outcome in the follow-up, was 2.0 ± 1.0 (SD) days, being in concordance with other reports [11, 16].

Discussion

The following changes occurred in our patient population with extension of the mean follow-up period from 17 to 37 months: 10 patients who had achieved undetectable PSA levels were entered in the various groups according to the disease outcome after at least 24 months. Of these, 9 patients showed no evidence of disease and 1 patient presented with rising PSA values. In all, 1 patient who had been classified as being cured after 10 months showed rising PSA levels after 14 months and was entered in the group of relapsed patients; 4 patients continued to show undetectable PSA levels but had not been monitored long enough to fulfill the criterion of at least 24 months of undetectable PSA levels for classification as being potentially cured at the time of this update; and 2 patients died of causes unrelated to prostatic carcinoma at 28 and 48 months after radical prostatectomy, respectively.

Increasing experience with PSA suggests that residual disease can be identified reliably on the basis of increased PSA levels during the monitoring of patients after radical prostatectomy [2, 6–8, 11, 16, 17]. Once a patient has achieved undetectable PSA levels, a rise in serum PSA precedes proof of persistent disease as diagnosed by conventional methods by a matter of months. Whereas the PSA half-life can be determined in the immediate postoperative period, a re-elevation of PSA as an indicator of re-

lapse occurred as late as at 19 months in the present follow-up period. Although we do not yet understand how residual tumor can produce enough PSA to prolong the half-life but fail to raise the PSA serum concentration above undetectable levels for weeks after surgery [12], the PSA half-life correlates significantly with the disease outcome, even in those patients who attain undetectable PSA levels but relapse as jugded by PSA re-elevation during the follow-up period.

All of the 10 patients whose PSA half-lives exceeded 3 days showed rising PSA levels within 19 months of follow-up, although 5 of those patients presented with undetectable PSA levels for an interval of 2–19 months postoperatively. Calculation of specificity and sensitivity for a cut-off of 2.7 days revealed 0.87 and 0.63, respectively. The results of this update reconfirm the findings obtained in the previous study. A mean postoperative PSA half-life of 1.6 days for "cured" patients can help to identify those patients who will present with a serological relapse during a long-term follow-up despite their having initially attained undetectable PSA levels. Whereas no correlation was found in the previous evaluation between PSA half-lives and time to recurrence, in this larger population a weakly negative correlation ($r = -0.273$; $P = 0.11$) was found: in patients whose PSA value declines to undetectable concentrations with long half-lives, serological relapse tends to occur earlier as compared with patients showing a more rapid decline.

In conclusion, relapse-free patients have a PSA half-life shorter than that reported for populations consisting of all patients who attain undetectable levels after radical surgery [8, 11, 16] and their half-lives differ significantly ($P < 0.02$) from those of patients who attain undetectable PSA levels but eventually relapse. Calculating the PSA half-life solely in patients in whom no evidence of residual disease had existed for at least 2 years, we found a mean half-life of 1.6 days.

Within the population of patients who attain undetectable PSA values, no criterion has been available for early identification of those who will relapse during the follow-up period. The use of serial serum PSA determinations for calculation of the PSA half-life after radical prostatectomy is a valuable predictive tool in advance of an absolute PSA re-elevation by up to 19 months. The PSA half-life is valuable in the management of apparently organ-confined prostate cancer to evaluate the completeness of tumor excision or the presence of residual distant disease. All patients with a PSA half-life of longer than 3.0 days proved to have serologically relapsed during the period of our follow-up despite their having achieved undetectable PSA levels following surgery.

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