Predictive Factors of Oncologic Outcomes in Patients Who do not Achieve Undetectable Prostate Specific Antigen after Radical Prostatectomy

Guillaume Ploussard, Frédéric Staerman, Jean Pierrevelcin, Rodrigue Saad, Jean-Baptiste Beauval, Morgan Roupret, François Audenet, Mickaël Peyromaure, Nicolas Barry Delongchamps, Sébastien Vincendeau, Tarek Fardoun, Jérôme Rigaud, Arnauld Villers, Cyrille Bastide, Michel Soulie, Laurent Salomon* and the Committee of Cancerology of the Association of French Urology

From the Departments of Urology and Andrology, Robert Debré Academic Hospital (FS, JP), Reims and Departments of Urology, Henri Mondor Academic Hospital (GP, RS, LS), Créteil, Groupe Hospitalier Pitié-Salpètrière (MR, FA) and Hospital Cochin (MP, NBD), Paris, Hospital Pontchaillou (SV, TF), Rennes, Hotel Dieu (JR), Nantes, Centre Hospitalier Universitaire Lille (AV), Lille, Hospital Nord (CB), Marseille and Centre Hospitalier Universitaire Rangueil (JBB, MS), Toulouse, France

Abbreviations and Acronyms

ADT = androgen deprivation therapy
EPE = extraprostatic extension
GS = Gleason score
PSA = prostate specific antigen
PSAV = PSA velocity
RP = radical prostatectomy
SVI = seminal vesicle invasion

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* Correspondence: Department of Urology, Centre Hospitalier Universitaire Henri Mondor, Ave. de Lattre de Tassigny, 94010 Créteil, France (telephone: +33 + (0) 1 49 81 25 53; FAX: +33 + (0) 1 49 81 25 64; e-mail: laurent.salomon@hmn.aphp.fr).

Purpose: We identified factors predicting oncologic outcomes in cases of persistently detectable prostate specific antigen.

Materials and Methods: We reviewed the charts of patients treated with radical prostatectomy between 1998 and 2011 at a total of 14 centers. Study inclusion criteria were radical prostatectomy for presumed localized prostate cancer, absent positive nodes and detectable prostate specific antigen, defined as prostate specific antigen 0.1 ng/ml or greater 6 weeks postoperatively. Of the 9,735 radical prostatectomy cases reviewed 496 (5.1%) were eligible for analysis. Predictive factors for oncologic outcomes were assessed in time dependent analyses using the Kaplan-Meier method and Cox regression models.

Results: At 6 weeks prostate specific antigen was 0.1 to 6.8 ng/ml. Biochemical progression was noted in 74.4% of patients and clinical metastasis was noted in 5%. The 2 most powerful predictors of general salvage treatment (vs radiotherapy) were postoperative prostate specific antigen greater than 1 ng/ml (OR 3.46, $p = 0.032$) and prostate specific antigen velocity greater than 0.2 ng/ml per year (HR 6.01, $p = 0.001$). Positive prostate specific antigen velocity was the single factor that independently correlated with the risk of failed salvage therapy (HR 2.6, $p = 0.001$). The 5-year disease-free survival rate was 81.0% in patients with stable or negative prostate specific antigen velocity compared with 58.4% in those with positive prostate specific antigen velocity ($p < 0.001$).

Conclusions: Patients with detectable prostate specific antigen after radical prostatectomy have a poor biochemical outcome. We identified postoperative prostate specific antigen and prostate specific antigen velocity as independent predictors of progression and failed salvage treatment. In addition to pathological prognostic factors, these factors should be considered early to better stratify patients for adjuvant therapy.

Key Words: prostate, prostatic neoplasms, prostatectomy, prostate-specific antigen, salvage therapy

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FAILURE to eliminate the primary tumor may result in local and general disease progression with subsequent distant metastasis, potentially leading to patient death. Six weeks after RP, postoperative PSA is expected to be undetectable, as dictated by its half-life.[1] Unfortunately, some patients fail to achieve undetectable PSA, interpreted as the presumption of cancer recurrence.[2]

This PSA persistence independently correlates with systemic recurrence-free and cancer specific survival, and is not just a surrogate marker for an adverse pathological condition.[3] However, the disease course in men with persistently detectable PSA after potentially curable surgery has not been well assessed. Residual benign prostatic tissue or extraprostatic tumor sites were also proposed as possible alternative sources of PSA to explain detectable postoperative PSA. These 2 hypotheses might show why some patients with detectable postoperative PSA have rapid clinical progression, while others may remain metastasis free during long-term followup. Literature data show that persistently detectable PSA is a strong, unfavorable predictive factor for subsequent biochemical and clinical disease progression.[4] Unfortunately, few specific series have been published. To date only 5 studies have been done to evaluate the natural history of patients in whom undetectable PSA is achieved immediately after surgery.[3,5–8] Moreover, only 2 groups have studied PSA kinetics as a potential predictive factor.[3,5]

In this retrospective multicenter study we examined the natural history and predictors of biochemical and clinical progression in patients with persistently increased PSA after RP.

MATERIALS AND METHODS

Patient Sample

Between 1998 and 2011 we retrospectively reviewed the charts of 9,735 patients treated with RP at a total of 14 centers. Study inclusion criteria were RP for presumed localized prostate cancer, detectable PSA (defined as PSA 0.1 ng/ml or greater 6 weeks postoperatively), absent positive lymph nodes and available postoperative ultrasensitive PSA assays. Patients treated with preoperative hormonal therapy or radiotherapy were excluded from analysis. Patients were required to have at least 2 PSA values separated by at least 3 months to have PSAV determined. A total of 496 cases (5.1%) fulfilled our inclusion criteria. Clinical, biological and pathological features were collected by a referring urologist at each center.

All patients were followed postoperatively according to French national guidelines with serial PSA determinations and clinical visits (at quarterly intervals in year 1, semiannually in year 2 and annually thereafter). Adjuvant or salvage treatments were proposed according to attending physician discretion in line with French national guidelines.

The study was done in accordance with Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

PSA Failure Definition and Treatment Plan

Persistent PSA was defined as failure to achieve PSA less than 0.10 ng/ml, as previously described.[3,5,8] PSAV was calculated by plotting PSA levels after surgery on the y axis and the interval after surgery on the x axis. Due to the PSA half-life of 3.15 days, we controlled PSA elimination kinetics after 6 weeks using the formula, $(\text{postoperative PSA}) = (\text{preoperative PSA}) \times \exp(-0.22t)$, where t represents days.[9] Thus, all preoperative serum PSA values in our study inevitably led to less than 0.10 ng/ml at 6 weeks.

Biological progression was defined as 2 consecutive PSA measurements greater than 0.2 ng/ml at least 3 months after RP. Salvage treatment failure was defined as biochemical and/or clinical progression.

Statistical Analysis

Predictive factors for biochemical progression after RP, salvage treatment type and failure, and overall mortality were assessed on time dependent univariate and multivariate analyses. Time dependent analyses included the Kaplan-Meier method and log rank test to compare survival curves according to potential predictive factors and a Cox regression model to assess independent values of study parameters and calculate the HR and 95% CI. The Harrell C statistic was used to assess model performance. Statistical analysis was done using SPSS® with statistical significance considered at $p < 0.05$.

RESULTS

Supplementary table 1 (http://jurology.com/) lists baseline patient cohort characteristics. Median preoperative PSA was 9.5 ng/ml. Pathological Gleason score was 8-10 in 19.1% of cases. EPE and SVI were reported in 45.4% and 20.4% of patients, respectively.

Supplementary table 2 (http://jurology.com/) lists followup data. At 6 weeks postoperatively PSA was 0.1 to 6.8 ng/ml (median 0.26). Biochemical progression was noted in 74.4% of patients a mean of 5.7 months after RP. Those with no diagnosis of recurrence were followed a median of 27 months. Of the patients 41 (8.3%) with immediately detectable PSA had an undetectable level 3 months after RP.

Salvage treatment was administered in 68.9% of patients and 13.9% underwent second line therapy after initial salvage failed. At the end of followup 70.1% of patients had no biochemical or clinical measurable disease, 25.1% had pure biochemical progression and in 5% progressive, clinically metastatic disease had developed.

On Pearson correlation analysis PSAV positively and significantly correlated with preoperative PSA