Original Study

Identification of Most Aggressive Carcinoma Among Patients Diagnosed With Prostate Cancer Using Mathematical Modeling of Prostate-Specific Antigen Increases

Félicité de Charry,[1,2] Olivier Colomban,[3] Benoit You,[1,3] Alain Ruffion,[4] Philippe Paparel,[4] Mélanie Wilbaux,[3] Michel Tod,[1,3] Gilles Freyer,[1,3] Paul Perrin[4]

Abstract

Mathematical models of prostate-specific antigen (PSA) longitudinal growth can help differentiate aggressive and indolent prostate cancer at diagnosis. The PSA kinetics of 62 patients with benign prostatic hyperplasia and 149 patients with prostate cancer were modeled. A modeled PSA growth rate kinetic parameter (RHO1) was associated with the probability of the D'Amico high-risk group and lower relapse-free survival.

Background: Tools for differentiating aggressive and indolent prostate carcinoma (PCa) are needed. Mathematical modeling is a promising approach for longitudinal analysis of tumor marker kinetics. **Patients and Methods:** The prostate-specific antigen (PSA) increases from patients with PCa and those with benign prostatic hyperplasia (BPH) were retrospectively analyzed using a mathematical model. Using the NONMEM program, individual PSA kinetics were fit to the following equation: $[d(PSA)/dt = (PROD.K \times \exp [RHO1 \times t]) \times (1 - BPH) + PROD.NK \times \exp (RHO2 \times t) - KELIM \times (PSA)]$, where RHO1 is the PSA production increase rate by PCa cells (PROD.K), RHO2 is the PSA production increase rate by non-PCa cells (PROD.NK), and KELIM is the PSA elimination rate. The comparative value of the modeled kinetic parameters, estimated for each patient, for predicting the D'Amico score and relapse-free survival (RFS) were tested using logistic regression analysis and multivariate survival tests. **Results:** The PSA kinetics from 62 patients with BPH and 149 patients with PCa before radical prostatectomy were successfully modeled. We identified statistically significant relationships between the PSA growth rate related to cancer cells (RHO1) and the probability of D'Amico high-risk group (less than the median RHO1 vs. at the median or greater: odds ratio, 2.15; 95% confidence interval [CI], 1.00-4.77; $P = .05$). RHO1 was also a significant prognostic factor for RFS on univariate analysis and against other reported prognostic factors using multivariate Cox tests. Three independent prognostic factors of RFS were found: RHO1 (hazard ratio [HR], 2.71; 95% CI, 1.25-5.84; $P = .01$), Gleason score (HR, 8.54; 95% CI, 4.19-17.40; $P < .01$), and positive surgical margins (HR, 2.04; 95% CI, 1.05-3.97; $P = .03$). **Conclusion:** Using a few PSA time points analyzed with a mathematical model (easily manageable in routine practice), it could be possible to determine before surgery whether a patient has presented with aggressive PCa.

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[1]Oncologie Médicale, Centre Hospitalier Lyon-Sud, Institut de cancérologie des Hospices Civils de Lyon (IC-HCL), Lyon, France
[2]Service de santé des Armées, Service de médecine interne et oncologie, HIA Desgenettes, Lyon, France
[3]EMR UCBL/HCL 3738, Faculté de Médecine Lyon-Sud, Université Claude Bernard Lyon-1, Université de Lyon, Lyon, France
[4]Département d'urologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Lyon, France

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Address for correspondence: Benoit You, MD, PhD, Oncologie Médicale, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Chemin du Grand Revoyet, Lyon 69495, France
E-mail contact: benoit.you@chu-lyon.fr

Introduction

With the increasing use of prostate cancer (PCa) screening and the prolongation of life expectancy,[1] an increasing number of PCa cases are being identified.[2] Autopsy studies have indicated that 30% of men aged > 50 years will have PCa, a proportion increasing to ≤ 75% at 80 years.[3] However, the estimated lifetime probability of developing a clinical diagnosis of PCa is only 16% in the United States.[4] A recent study reported that 1055 men would be screened and 37 treated to prevent 1 prostate cancer death.[5] The treatments currently available for men with localized PCa include variable approaches such as watchful waiting, radical prostatectomy, radiation

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therapy, or focal therapy. The choice among the procedures depends on several criteria, including patient prognostic factors, physician convictions, and patient preference regarding the risk of adverse events.[6] The treatment choice would be facilitated by the identification of the aggressive cancer fraction, which has been associated with poor survival, among all PCa cases.[6]

To date, the established clinical parameters used in the PCa setting, such as prostate-specific antigen (PSA) level, digital rectal examination findings, and biopsy with Gleason score, have failed to accurately predict PCa aggressiveness.[7] A recent report by Ilic et al[8] concluded that screening did not significantly reduce PCa-specific mortality, justifying the need for new markers of PCa aggressiveness.

Several predictive and prognostic tools (eg, reference tables, classification and regression tree analyses, new biomarkers, artificial neural networks, and nomograms) have been developed to assist physicians in the clinical decision-making process.[9] However, none has been validated for routine use. Longitudinal analysis of PSA kinetics using mathematical modeling might help differentiate the PCa cases portending a very poor prognosis, just as it did in postoperative period.[10,11] Longitudinal analysis of other serum tumor markers could also be useful.[12] A mathematical modeling approach enables the description of biologic phenomena, such as the time changes of drug concentrations or biomarker titers, using sets of mathematical equations. Prognostic kinetic parameters can be derived from such analyses.[12] This strategy has never previously been used for analysis of preoperative PSA kinetics.

The present retrospective study aimed to assess the relationships between longitudinal preoperative PSA kinetics assessed using mathematical modeling and D'Amico score or relapse-free survival (RFS).

Patients and Methods

Patients and Objectives

The data from 211 patients consecutively monitored for prostate disease (BPH or localized PCa) at a French hospital (Centre Hospitalier Lyon-Sud, Lyon, France) from 1997 to 2015 were used. We included patients with both PCa and BPH in the analysis to discriminate PSA production by PCa tissue and benign prostate tissue using modeling. PSA assays were collected every 3 to 6 months for all patients.

If PCa was diagnosed, radical prostatectomy was performed, potentially to be followed by adjuvant radiotherapy and/or hormone therapy in the case of a Gleason score of ≥ 8, stage $>$ pT3, positive surgical margins, or lymph node involvement. The preoperative prostate volumes were estimated from ultrasound scans. The D'Amico risk was calculated using the PSA value, biopsy Gleason score, and clinical stage at diagnosis.[6] All the patients with PCa and all those with BPH included in the present study were required to have ≥ 2 preoperative PSA measurements.

If the patients had BPH, they underwent regular monitoring of PSA values and intraurethral prostate resection in the case of symptomatic obstruction.

The primary objective of the present retrospective study was to show the feasibility of characterizing the longitudinal preoperative PSA kinetics from patients with BPH or PCa using a population kinetic semimechanistic model. The secondary objective was to identify the modeled kinetic parameters related to preoperative PSA dynamics (PSA production, PSA elimination) that might provide early predictive value regarding D'Amico risk or RFS.

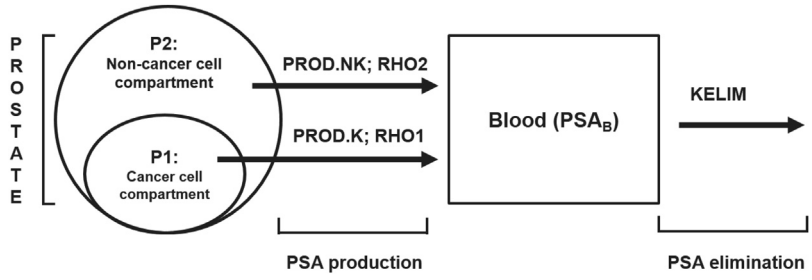
PSA Velocity

The PSA velocity was calculated using linear regression analysis of the last 4 annual PSA values before surgery in both cohorts.[13]

Model Building

The individual preoperative PSA data were analyzed using a population kinetic approach and a semimechanistic nonlinear mixed effect model frequently used for pharmacokinetic studies (Figure 1).[14,15] This approach provides a unique model to describe all observed profiles. The basic details of the population kinetic approach are presented in Supplemental Appendix 1 (available in the online version). PSA productions induced by PCa and BPH were expressed by a multiexponential model.[16] This model is expressed as follows:

Figure 1 Description of Semimechanistic Model. The Prostate is Composed of 2 Zones: the Cancer Cell Compartment (P1) and the Noncancer Cell Compartment (P2)



Abbreviations: KELIM = PSA elimination rate (velocity; days); PROD.K = PSA production by P1 (IU/d); PROD.NK = PSA production by P2 (IU/d); PSA = prostate-specific antigen; PSA_B = PSA concentrations in the blood (ng/mL); RHO1 = PSA production increase rate by P1 (days); RHO2 = PSA production increase rate by P2 (days).