Development and validation of a model of PSA kinetics predicting prostate cancer aggressiveness during screening

LE SAUX Olivia (1, 2), YOU Benoît (1, 2), HENIN Emilie (1), PIERRILLAS Philippe (1), PERRIN Paul (3), RUFFION Alain (3), BONIOL Mathieu (4), FREYER Gilles (1, 2), TOD Michel (1), COLOMBAN Olivier (1)

(1) EMR 3738 CTO, UCBL - HCL Faculté de Médecine Lyon-Sud, Université Lyon 1, Oullins, France. (2) Medical Oncology Unit, Centre Hospitalier Lyon Sud, Pierre-Bénite, France.
(3) Urology Department, Centre Hospitalier Lyon Sud, Pierre-Bénite, France. (4) Strathclyde Institute of Global Public Health, Biostatistics, International Prevention Research, Lyon, France.

Introduction

- Prostate cancer (PC) is the **most common cancer** among men [1].
- A growing number of cancers is detected by screening.
- Tools to distinguish aggressive and indolent tumors are necessary to avoid over-diagnosis and overtreatment.

Objectives

To develop a kinetic model of PSA (Prostate-Specific Antigen), a protein produced by the prostate gland, to differentiate the aggressive PCs among screened PCs.

Patients & Methods

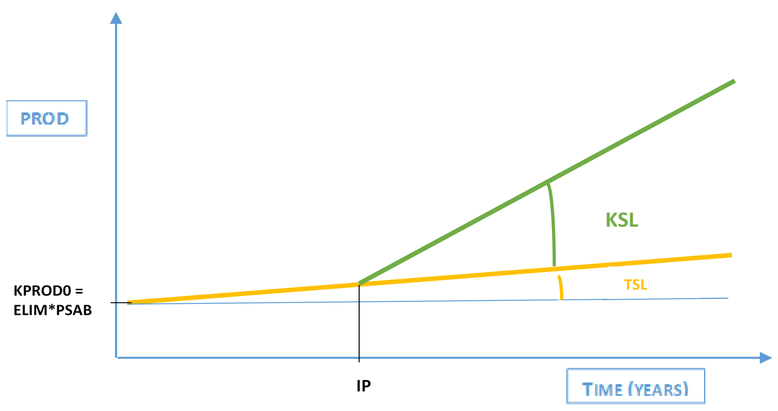
Patients

- Data: **American PLCO trial** [2].
- Between 1993 and 2011, 38343 men aged 55-74, enrolled in 10 study centers across the United States, were randomized to annual PSA screening for 6 years.
- In order to achieve reasonable computation times, **we randomly selected 500 patients stratified on cancer status**.
- Aggressiveness of PC was defined as: biopsy Gleason score ≥7, and/or clinical stage ≥III, and/or fatal [3].

Methods

- Individual pre-operative log-transformed PSA data were analyzed with a semi-mechanistic non-linear mixed effect model allowing the estimation of inter-individual variability on each parameter, using NONMEM 7.3.
- PSA kinetics were best described by a turn-over model with first order elimination. PSA production was differentiated in 2 subpopulations using "Mixture subroutine" (Figure 1) :
  - ➢ Sub-population 1: linear increase with time (TSL) corresponding to the natural increase of PSA production with age.
  - ➢ Sub-population 2: from a given time IP, production may be increased by cancer (KSL).

Figure 1. Production Modeling.

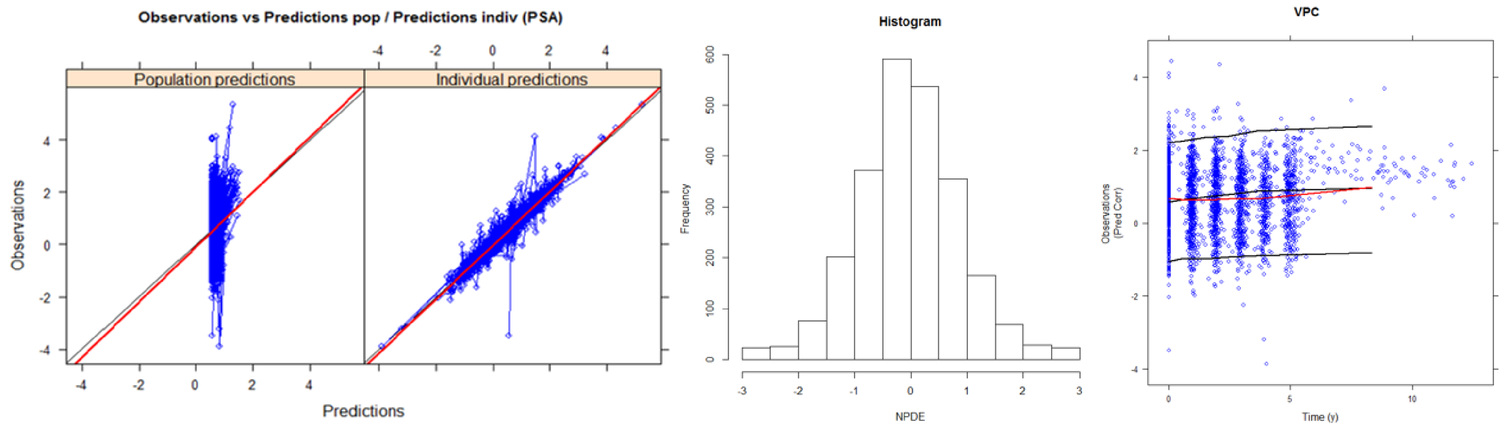


The model is as follows:
dPSA/dt = PROD – ELIM*PSA
PSA(t=0) = PSAB
Sub-Population 1: PROD = KPROD0 + TSL*t
Sub-Population 2:
- t<IP: PROD = KPROD0+ TSL*t
- t>IP: PROD = KPROD0+ TSL*t + KSL*(t-IP)

Results

Model evaluation

- **Goodness-of-fit plots** and **VPC** were as follows:



- **Parameter values** are reported in Table 1.

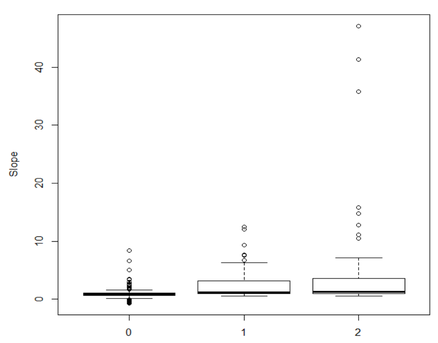
Table 1. Parameters Estimates.

Model and Values	TSL (yr^{-1})	ELIM (yr^{-1})	PSAB (ng)	IP (yr)	KSL (yr^{-1})
TYPICAL VALUES					
Estimate	0.91	6.36	1.77	3.99	0.98
RSE (%)	8.72	14.1	4.63	17.5	53.4
COEFFICIENT OF VARIATION					
Estimate (%)	71.8	133	95.0	39.8	178
RSE (%)	8.53	8.76	3.40	33.2	26.3

Correlation to PC aggressiveness

- Production slopes according to cancer and aggressiveness status are reported in Figure 2.
- The **production slope (TSL+KSL)** was significantly associated with cancer aggressiveness (p=0.05) by logistic regression.

Figure 2. Boxplot of production slopes according to cancer and aggressiveness.



Conclusion and perspectives

- Our semi-mechanistic model describes PSA kinetics in 500 patients and the production slope correlates with aggressiveness.
- **Perspectives**: Model building on the entire population (n=38343) and correlation with PC aggressiveness.
- If relationships between kinetic parameters and PC aggressiveness were demonstrated, it would provide an interesting tool for distinguishing the most aggressive tumors among screened PC and for adjusting treatment delivered to patients.

References and ackowledgements

[1]. Howlader N et al., SEER Cancer Statistics Review (CSR) 1975–2010. National Cancer Institute Website.
[2]. Andriole GL et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med, 2009. 360(13): p. 1310-9.
[3]. Zhou CK et al. Relationship between male pattern baldness and the risk of aggressive prostate cancer: an analysis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. J Clin Oncol. Feb 10 2015;33(5):419-425.

We thank the « Fondation pour la Recherche Médicale » for their financial support (File code : DEA20140630441).