

Monitoring Blood Prostate-Specific Antigen (PSA) after Radical Prostatectomy

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INTRODUCTION

- PSA is the main biomarker used to detect prostate cancer relapse after prostatectomy, and its monitoring is recommended in current guidelines for the management of patients.
- PSA doubling time (PSADT) is a useful concept to assist PSA results interpretation. However, several calculation options compete, and there is no consensus regarding how to best assess PSA kinetics.
- The aim of this retrospective observational study was :
 - to describe PSA trajectories, prognostic markers (TNM grade, Gleason score, capsular penetration), and progression free survival after radical prostatectomy;
 - to assess critically the various PSADT calculations for their predictive performance regarding relapse.

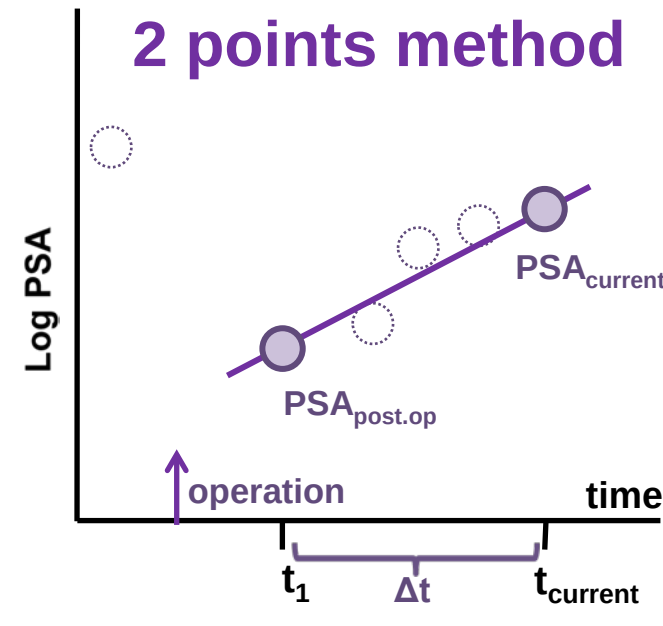
METHODS

- PSA data collection:** Laboratory Meditest, Vevey (Switzerland)
- Inclusion criteria:** PSA levels (ng/mL) regularly monitored in patients after radical prostatectomy (i.e. $\geq 3x$ in 1 year or $4x$ in 2 years)
- Clinical data collection:** Data extraction from medical records (general practitioners and urologists)
- Study variables:**
 - From Meditest: All PSA values (ng/mL) and dates of measurements from included patients
 - From patients records : Primary outcome; remission versus relapse status; dates of interventions; Gleason score; pTNM stage; capsular penetration; subsequent biopsies; imaging; chemotherapy, radiotherapy or hormonal treatment
- Relapse:** Defined by distant metastasis or biopsy and imagery showing local recurrence or secondary anticancer treatment
- PSADT calculations:**
 - 2 points method:** arithmetic calculation (Δt = time difference in years)

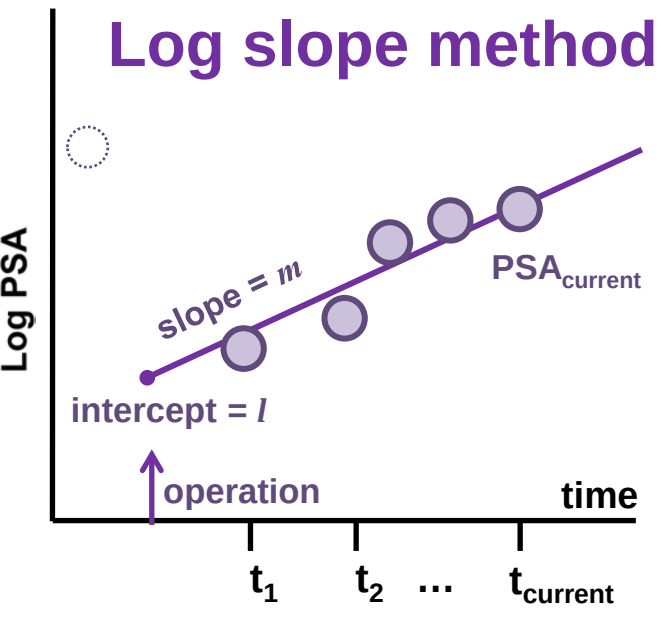
$$\frac{\text{Log}(2) \cdot \Delta t}{\text{Log}(PSA_{current}) - \text{Log}(PSA_{post-op})}$$
 - Log slope method:** $\frac{\text{Log}(2)}{m}$ m = slope from individual regression: $\text{Log}(PSA_{current}) = l + m \cdot t$
 - Bayesian method:** $\frac{\text{Log}(2)}{g_i}$ g_i = post-hoc individual rate constant for late re-growth after longitudinal non-linear mixed effect model (NONMEM) according to Stein & al. (Clin Cancer Res. 2011;17:907-17)

$$PSA = PSA_{preop_i} (e^{-d_i \cdot t} + e^{g_i \cdot t} - 1)$$

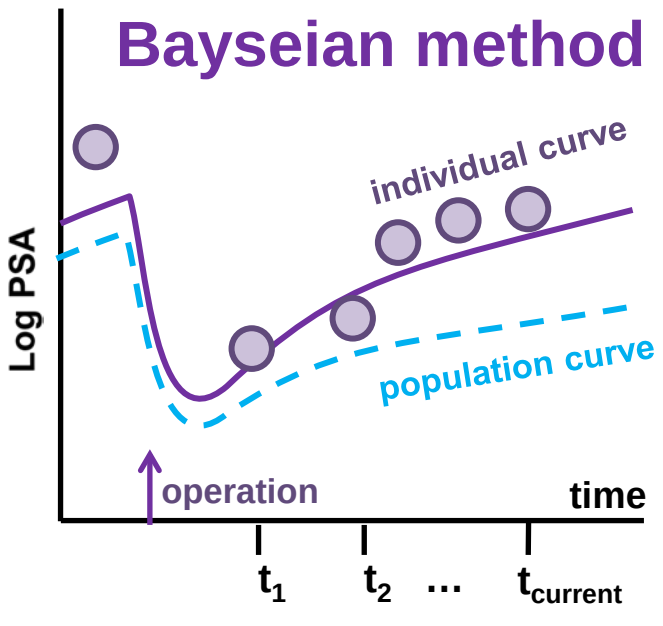
2 points method



Log slope method



Bayesian method

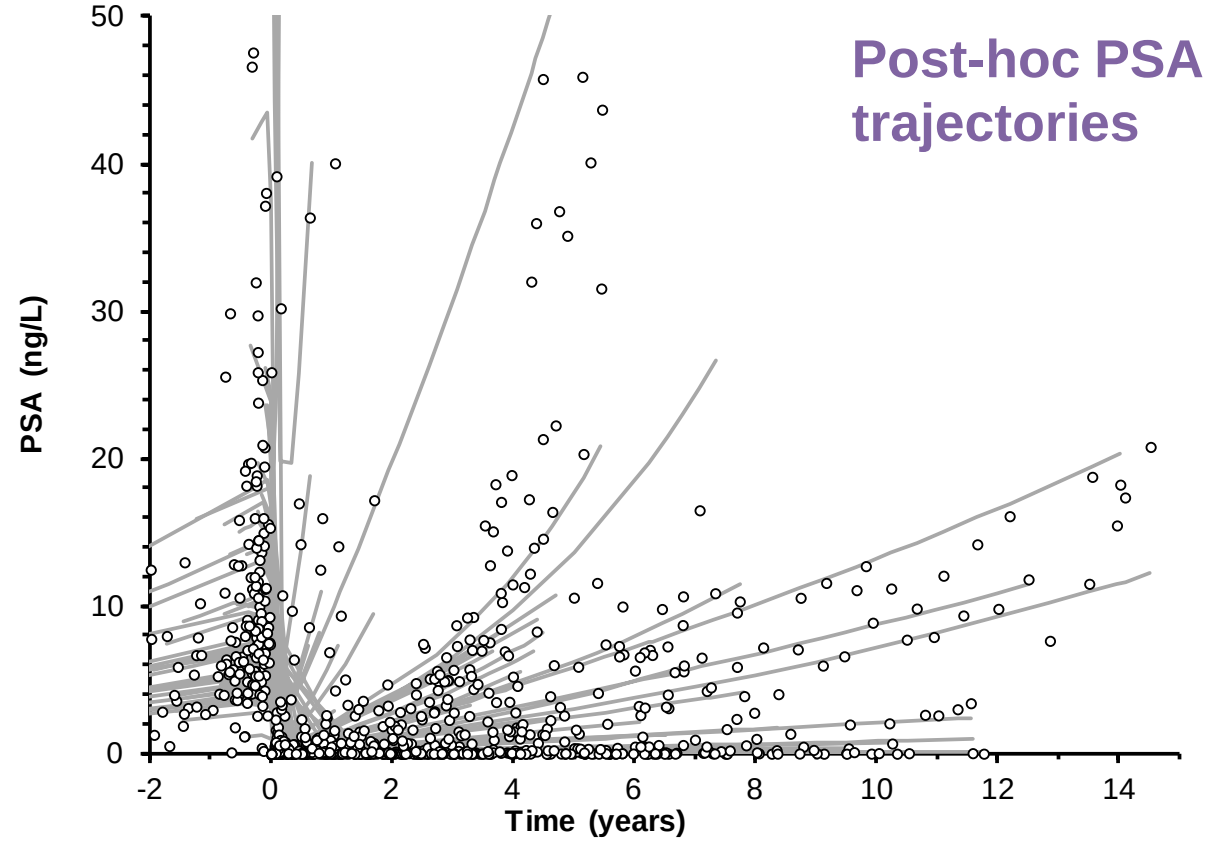

- Time window:** calculations with PSA results collected ≤ 1 , ≤ 2 , ≤ 3 and ≤ 5 years after operation
- Concentration window:** calculations done once with all values, and once only with PSA ≥ 0.1 ng/mL (as recommended by several authors)
- Statistics:**
 - Relationships between prognostic markers and relapse: survival analysis with Cox proportional hazard models, compared by likelihood ratio tests (STATa)
 - Prognostic contribution of PSADT: sequential inclusion into the survival model of 1/PSADT calculated various ways, with different time and concentration windows

POPULATION & PSA

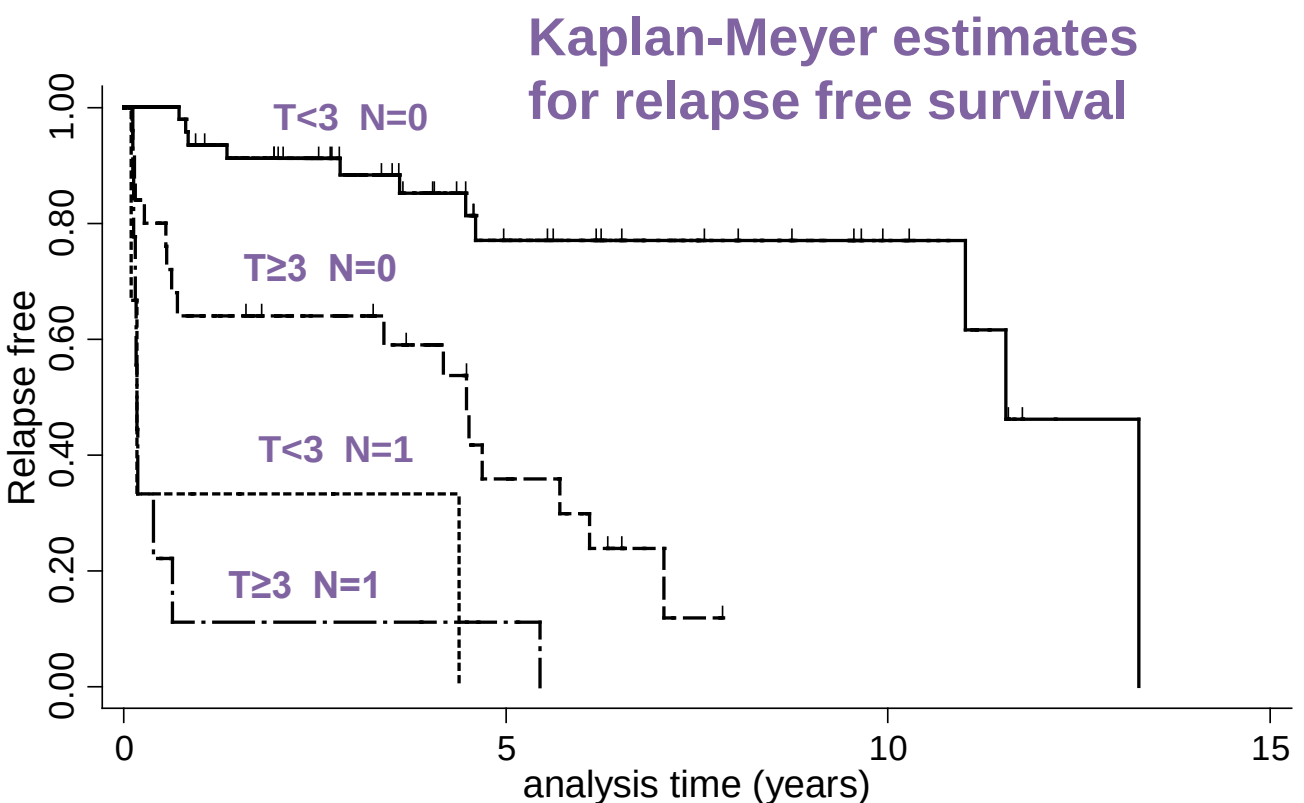
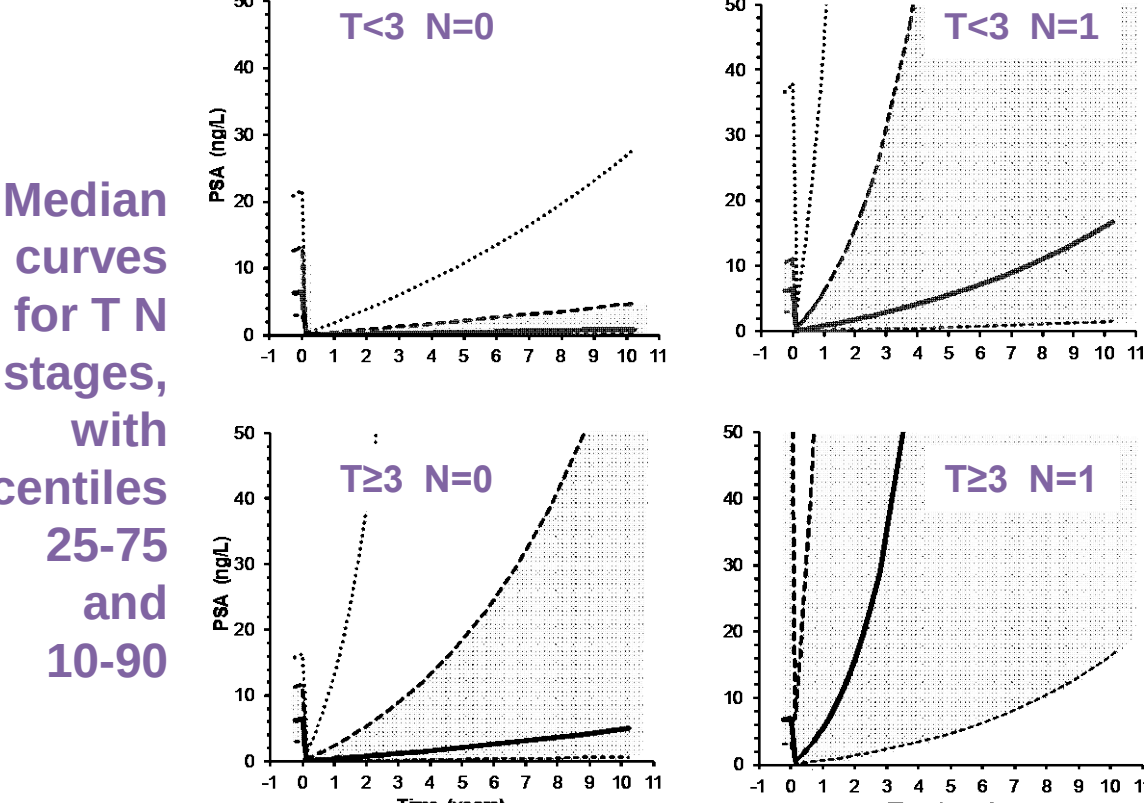
Number of patients	102
Median follow-up (range)	5 (1-16) years
Men age at PC diagnosis (range)	66 (50 – 80) years
Patients with relapse after Radical Prostatectomy	52
Patients with T stage > T2b at diagnosis	49
Patients with Gleason score > 6 at diagnosis	53
Patients with Nodal invasion at diagnosis	12
Median PSA measurements per patient (range)	16 (5-45)

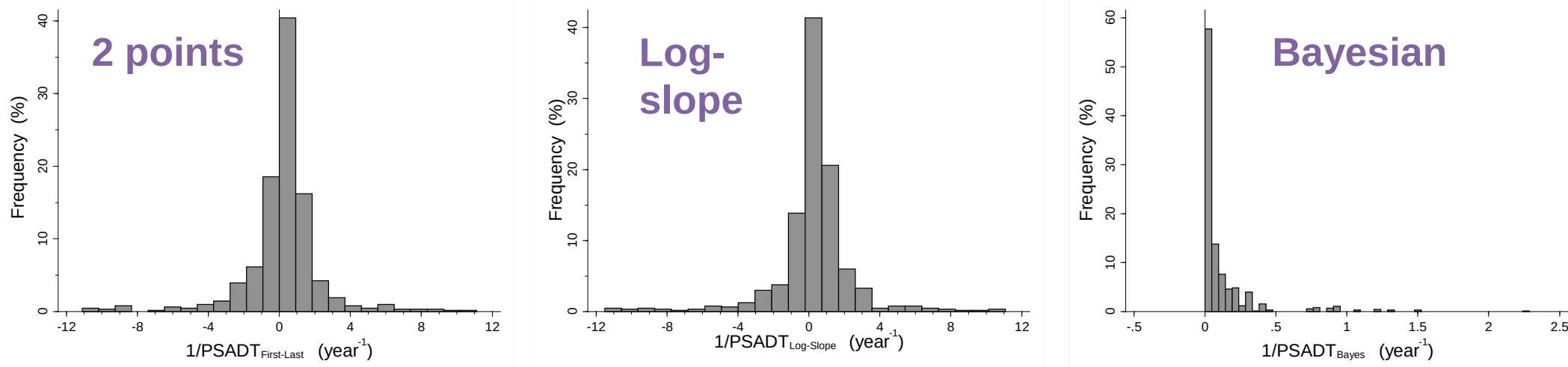
RESULTS

- Log-transformed PSA trajectories described with NONMEM are fairly curvilinear within patients, but highly variable and divergent between patients. T and N stage at operation significantly affect PSA regrowth rate.



Parameter	Estimate	Variability
PSA _{preop}	6.99	84%
Drop rate d	50.9	51%
Growth rate g	0.0106	210%
factor for T ≥ 3	5.14	
factor for N=1	11.27	
Proportional σ		55%
Additive σ		0.031
- All tumoral markers are strong predictors of relapse ($p < 0.001$). Multivariate combination though only retains T and N stages as significant (T $\geq 3a$: hazard ratio [CI95%] = 5.1 [2.4-10.9]) (N=1: HR = 3.9 [1.9-8.2])



- PSADT calculation methods give remarkably different results.


- The log-slope and Bayesian PSADT improve relapse prediction over T and N stage. Log-slope worsens but Bayesian improves over time. Taking into account all PSA values is more efficient than selecting those ≥ 0.1 ng/mL.

Calculation	≤ 1 y	≤ 2 y	≤ 3 y	≤ 5 y
HR for PSADT 2 points	1.03 <i>ns</i>	1.03 <i>ns</i>	1.04 <i>ns</i>	1.06 <i>ns</i>
HR for PSADT log-slope	1.31 $p=0.03$	1.25 <i>ns</i>	1.05 <i>ns</i>	1.08 $p=0.06$
HR for PSADT Bayesian	1.28 <i>ns</i>	11.14 $p=0.002$	11.59 $p=0.0019$	12.40 $p=0.0013$

CONCLUSION

- PSA trajectories are characterized by large variability, even accounting for known prognostic markers.
- Tumor grades T and N are the strongest predictors of both PSA trajectories and cancer relapse (evidently correlated!).
- PSADT calculated by the log slope method improves the early prediction of relapse at 1 year. All PSA values should preferably be used, including those < 0.1 ng/mL.
- Bayesian PSADT calculation introduces impressive shrinkage; it offers little advantage for early relapse prediction, but its prognostic/diagnostic value improves over follow up time.
- Our results fully support the regular follow-up of PSA and calculation of PSADT for detection of cancer relapse after radical prostatectomy.

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