CISNET-Prostate Group

PERSONALIZED BIOPSY SCHEDULES USING CAUSE-SPECIFIC INTERVAL-CENSORED JOINT MODELS

Zhenwei Yang[1], Dimitris Rizopoulos[1], Eveline A.M. Heijnsdijk[2], Lisa F. Newcomb[3], and Nicole S. Erler[1]

[1]Department of Biostatistics - Erasmus MC; [2]Department of Public Health - Erasmus MC; [3]Fred Hutchinson Cancer Research Center

z.yang@erasmusmc.nl

Introduction

- **Active Surveillance** (AS) is implemented for patients with low-risk prostate cancer to reduce overtreatment.
- However, regular biopsies in AS are burdensome for patients.

Example AS programs (Canary PASS Trial)

- **Examinations**:
  - PSA tests every 6 months
  - Biopsies at year 0.5, 1, 2 and afterward biennially
- **Endpoints**:
  - 183 (of 833) patients experienced cancer progression.
  - 87 (of 833) patients initiated treatment in absence of progression.

- We propose a methodology of scheduling biopsies based on the progression-specific risk and a risk threshold to avoid unnecessary biopsies, i.e., **personalized biopsy schedules** (see Fig. 1).

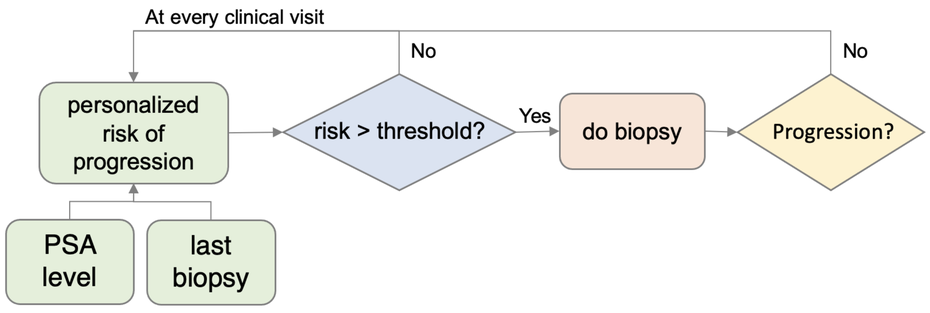

Figure 1: Flowchart of a personalized biopsy schedule.

Method

Cause-specific interval-censored joint model (CIJM)

To estimate the patient's individual risk of progression, joint models for longitudinal and time-to-event data are used. Furthermore, the cause-specific interval-censored joint model (CIJM) is proposed.

CIJM handles two challenges:

1. Competing risk from initiating treatment
2. Interval censoring due to periodical biopsies

Longitudinal submodel

The longitudinal component that models the underlying subject-specific trajectory of PSA levels is able to correct for measurement error.

$$\log_2(\text{PSA}_i + 1)(t) = m_i(t) + \epsilon_i(t)$$

$$m_i(t) = \beta_0 + b_0 + \underbrace{\sum_{w}^{3}(\beta_w + b_w)\mathcal{C}_i^{(w)}(t)}_{\text{natural cubic splines}} + \underbrace{\beta_4(\text{Age}_i - 62)}_{\text{baseline covariate}}$$

where $\mathcal{C}(t)$is the design matrix for the natural cubic splines for time t; the error term $\epsilon_i(t) \sim t_3$.

Survival submodel

The PSA levels derived from the longitudinal submodel are used to estimate the risk of progression. Taking the competing risk into account, a cause-specific proportional hazard model is used. The hazard of experiencing event k (k = 1 denotes progression; k = 2 denotes treatment) is:

$$h_i^{(k)}(t \mid \boldsymbol{\mathcal{M}}_i(t)) = h_0^{(k)}(t)\exp\left\{\gamma_k \text{density}_i + \alpha_{1k} m_i(t) + \alpha_{2k}\left[m_i(t) - m_i(t-1)\right]\right\}$$

where $\boldsymbol{\mathcal{M}}_i(t)$ is the estimated true history of PSA levels for subject i; $m_i(t)$ and $m_i(t) - m_i(t-1)$ is the estimate of the PSA level and yearly PSA change for subject i at time t, respectively.

Personalized schedules

Using the estimated risk profile from CIJM and a pre-specified cut-off for this risk, say, 8%, we can create a personalized biopsy schedule for each patient. In Fig. 2, two example personalized schedules with updated information of PSA measurements are presented ⇒ the methodology of personalized schedules has a **dynamic nature** (Scan the QRcode for a demo).

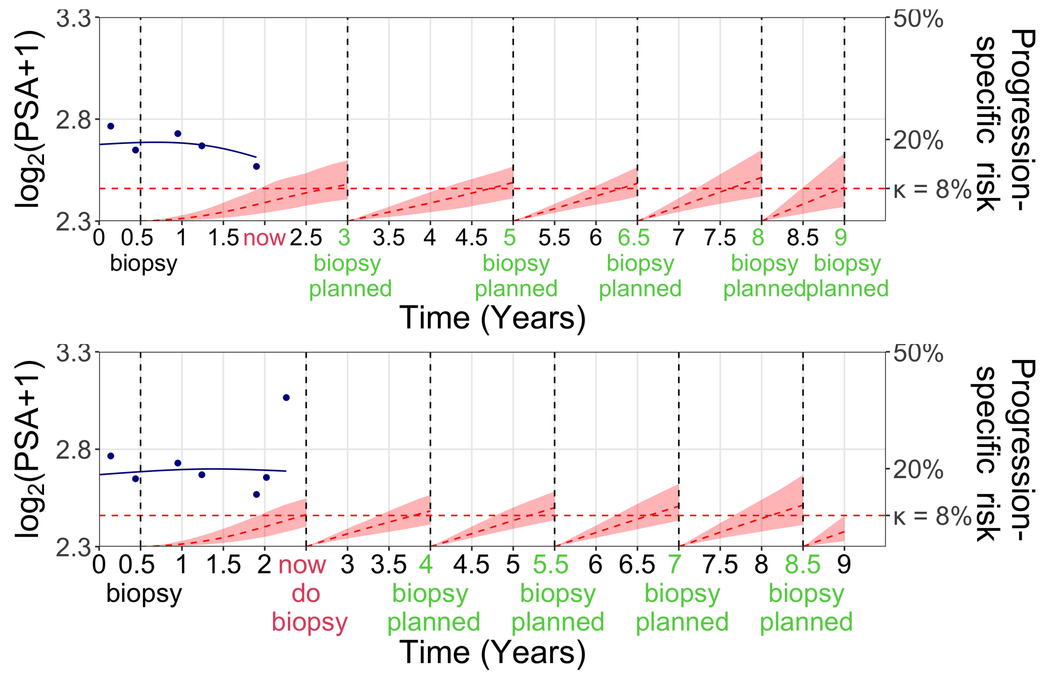

Figure 2: Example of personalized schedules with a risk threshold of 8%.

Different pre-specified thresholds (κ) result in different **number of biopsies** and **detection delay** for each patient. Higher thresholds can reduce the number of biopsies but cause longer detection delay. The optimal threshold can be chosen by balancing the two aforementioned indicators.

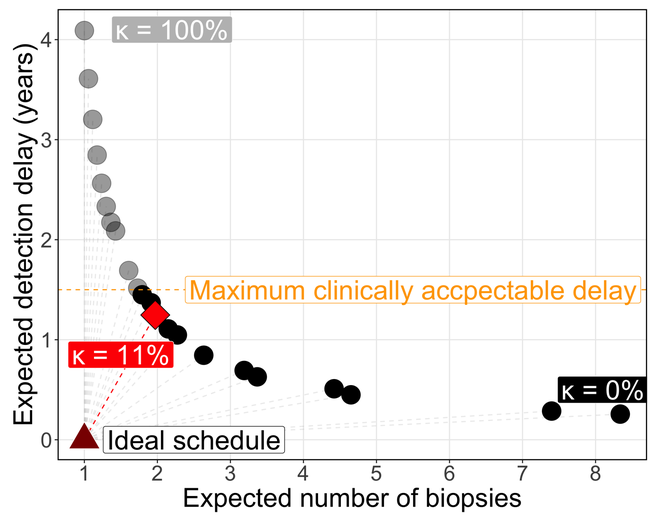

Figure 3: Choice of the optimal risk threshold based on the expected number of biopsies and detection delay.

Simulation

We compared the personalized schedules with a schedule of annual biopsies and a schedule under the PASS protocol based on number of biopsies and detection delay. Our personalized schedules can **reduce the number of biopsies by more than 50%** compared to the fixed schedules, both for patients with and without progression. As a trade-off, personalized schedules lead to **moderately longer detection delay**.

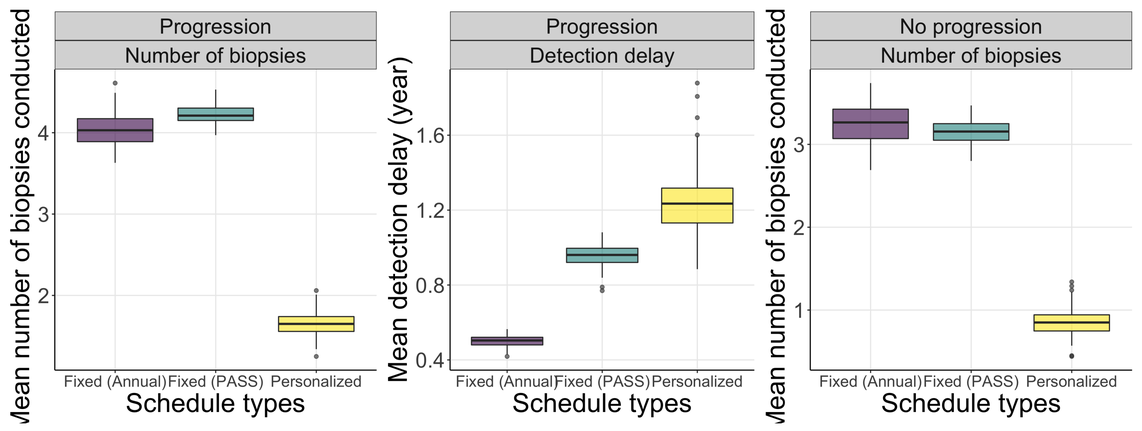

Figure 4: Simulation results for evaluating AS schedules.