Personalized Risk Based Shared Decision Making Framework for Biopsies in Prostate Cancer Active Surveillance[☆]

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Abstract

`Background`: Low-risk prostate cancer patients enrolled in active surveillance undergo repeat biopsies. Treatment is provided upon detection of biopsy Gleason upgrade.

`Objective`: Reduce the number of biopsies for patients who do not need them

`Design, Setting, and Participants`: adadadad

`Outcome Measurements, and Statistical Analysis`: adadadad

`Results and Limitations`: adadadad

`Conclusions`: adadadad

[☆]Word Count Abstract: 300; Word Count Text: 2800

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`Patient Summary`: adadadad

Keywords: Active Surveillance, Biopsies, Personalized Medicine, Prostate Cancer, Shared Decision Making

1. Introduction

Patients with low- and very low-risk screening-detected localized prostate cancer (PCa) are usually advised active surveillance (AS) instead of immediate radical treatment [1]. In AS, PCa progression is routinely monitored via prostate-specific antigen (PSA), digital rectal examination, and the Gleason score from repeat prostate biopsies. Among these, the Gleason score is the strongest indicator of cancer related outcomes. Thus, patients are commonly advised curative treatment upon disease reclassification [2], which is detected via upgrade in biopsy Gleason score.

Since biopsies are scheduled intermittently, disease reclassification is always detected with a delay. The smaller the delay is, the larger is the window of opportunity for curative treatment. To this end, majority of the AS programs worldwide, schedule biopsies every 12-24 months for all patients [3, 4]. Such fixed and frequent biopsies may benefit a small proportion of men with a high risk of reclassification. However, for many of the *slow progressing* patients (see Figure 1) frequent biopsies are redundant . Biopsies are also invasive, painful and prone to medical complications. The unnecessary burden of biopsies, and patient non-compliance [5] to frequent biopsies, has raised questions about the optimal time interval between subsequent biopsies [6, 7].

The simplest solution to frequent biopsies is reducing the frequency of biopsies for all patients. However, simulation studies have suggested that reducing the frequency beyond 24 months may not leave sufficient window of opportunity for curative treatment [6]. Although, with a gap of 24 months up to five unnecessary biopsies over ten years of follow-up may still be scheduled for the *slow progressing* patients. A promising alternative to such fixed rules

is biopsy decisions based on the risk of reclassification. Consider for instance the two patients shown in Figure 2. Both patients had their latest biopsy at year one of follow-up and are now scheduled for a biopsy after a 24 month gap at year three. The PSA profile of patient A is stable and the PSA profile of patient B is rising. Since the risk of reclassification for patient A (vice-versa for patient B) is very low, he may not be subjected to unnecessary biopsy at year three.

The first challenge in the risk based approach is consolidation of observed patient data. An approach is to combine information from PSA profile with the results of previous biopsies to provide an estimate of the risk of reclassification (Figure 2). To this end, previous studies have employed joint models for time-to-event and longitudinal data [9, 10, 11]. A subsequent challenge however, is to translate these risk estimates into decisions of biopsy (or wait). A 10% risk can be perceived as high or low depending upon the patient's age and comorbidities. In order to make decisions patients not only require estimates of the risk, but also the estimates of consequences of a decision. Two important consequences are the delay in detection of reclassification, and the total burden of biopsies. As with the risks the consequences should also be personalized, and should be dynamically updated as more data is gathered over follow-up. Thus a complete framework for shared decision making of biopsies is required.

The goal of this work is to help patients and doctors make better decisions of biopsies than fixed and frequent biopsies. To this end, we first fit a prediction (joint) model to the world's largest AS dataset, PRIAS. Subsequently, we validate our model in multiple external cohorts that are part of

the GAP3 database. Using the personalized risk predictions, we then propose the aforementioned framework for shared decision making of biopsies. Lastly, we implement the decision making framework as a web-application, and demonstrate it with real patient data.

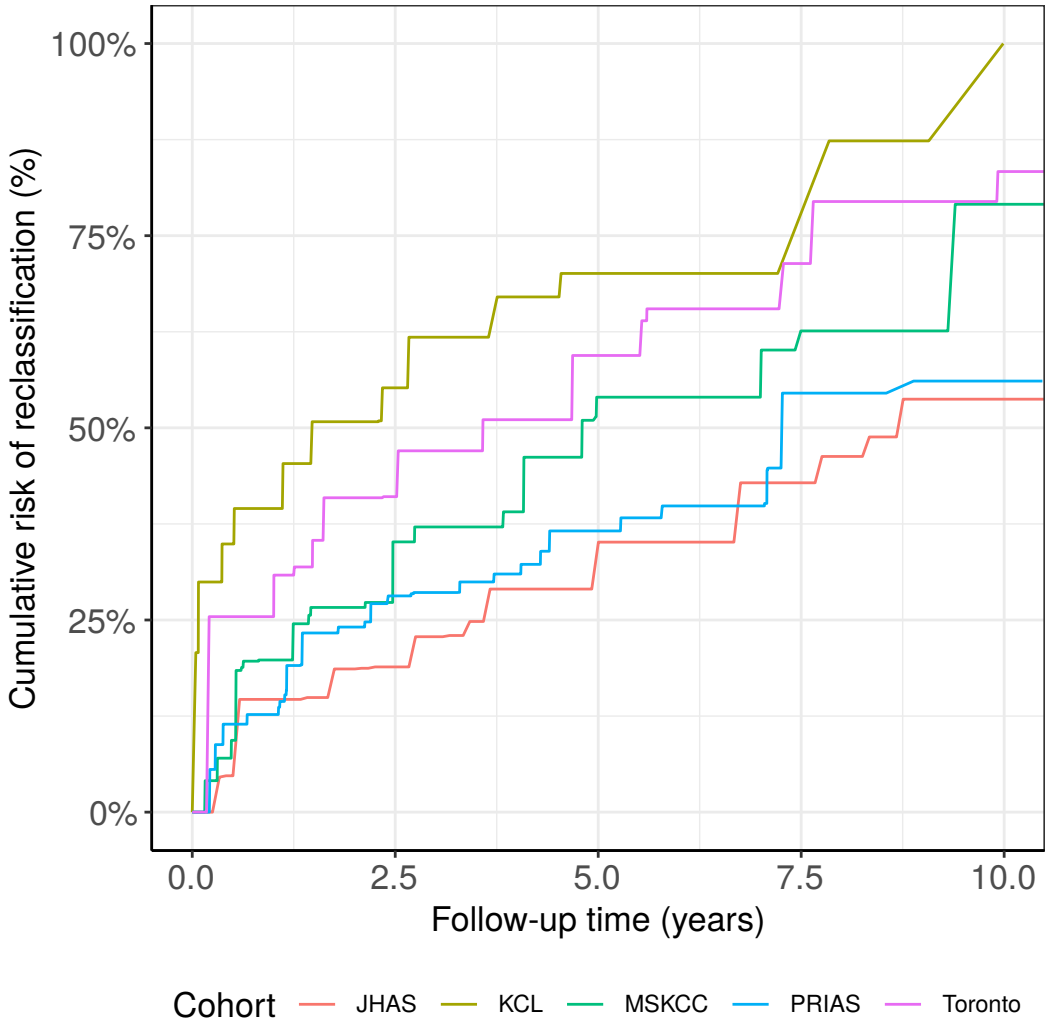

Figure 1: **Active Surveillance Cancer Patients Are Often *Slowly Progressing***. Graph shows estimated cumulative risk of reclassification[2] in AS in five of the largest AS studies that are part of the GAP3 database [8]. In all cohorts except KCL, roughly 50% patients do not require any biopsy in first five years. In the world's largest AS cohort PRIAS and in JHAS, roughly 50% patients do not require any biopsy in the first ten years. **Legend**: *JHAS*: Johns Hopkins Active Surveillance, *PRIAS*: Prostate Cancer International Active Surveillance, *Toronto*: University of Toronto Active Surveillance, *MSKCC*: Memorial Sloan Kettering Cancer Center Active Surveillance, *KCL*: King's College London Active Surveillance

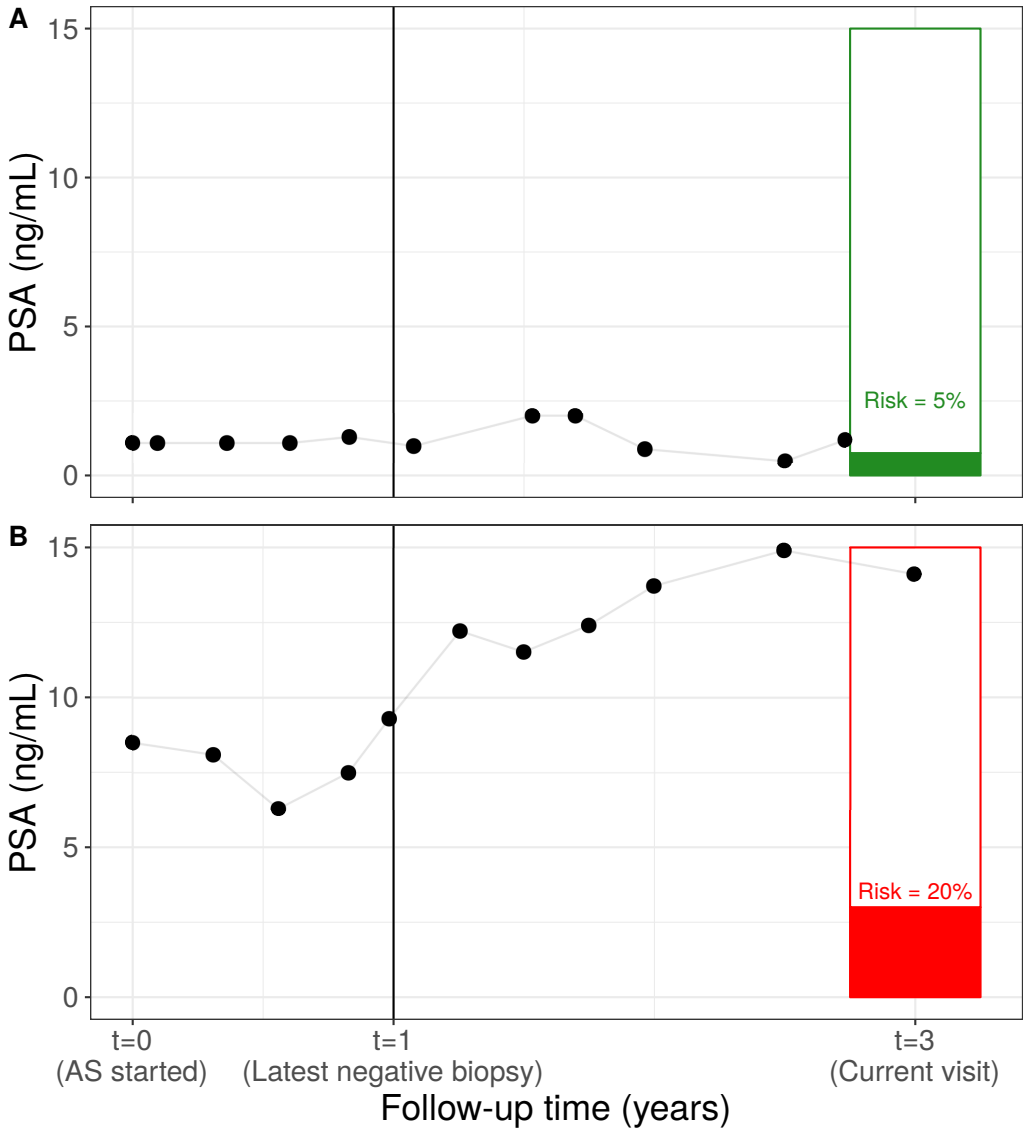

Figure 2: **Motivation for risk based decisions of biopsy**: Patient A and B had their latest biopsy at year one of follow-up. Patient A's prostate-specific antigen (PSA) profile remained stable until the current visit time at year three. Consequently, his cumulative risk of reclassification at year three is 5%. On the other hand patient B's PSA profile has shown a rise since the latest biopsy, and his cumulative risk of reclassification is also 20%. Patient B is a better candidate for biopsy than Patient A.

2. Patients and Methods

2.1. Study Cohort

Prostate Cancer International Active Surveillance (PRIAS) is an ongoing prospective cohort study of men with low- and very-low risk PCa diagnoses [2]. More than 100 medical centers from 17 countries worldwide contribute to the collection of data, utilizing a common study protocol and a web-based tool, both available at `www.prias-project.org`. We use the data collected over a period of ten years (Table 1), between December 2006 (beginning of PRIAS study) and December 2016. The follow-up protocol scheduled PSA measurements every three months for the first two years and every six months thereafter. Repeat biopsies were scheduled after one, four, seven, and ten years. In addition for patients having PSA doubling time (PSA-DT) between three years and ten years, yearly repeat biopsies were advised. Patients were recommended treatment upon disease reclassification, which is defined as more than two positive cores or Gleason > 6 at repeat biopsy. Due to the periodical nature of biopsies, the true time of disease reclassification remained unknown. However, the time interval in which it occurred was available.

In this paper, the event of interest is disease reclassification. There are three types of competing events, namely death, removal of patients from AS on the basis of PRIAS protocol, and loss to follow-up. However, we focus only on reclassification and consider other events as censored, because reclassification is the trigger for treatment advice.

Table 1: **Patient characteristics for the PRIAS dataset**. The primary event of interest is disease reclassification. IQR: interquartile range, PSA: prostate-specific antigen.

Characteristic	Value
Total patients	5270
Disease reclassification (primary event)	866
Loss to follow-up (anxiety or unknown)	685
Patient removal on the basis of protocol	464
Death (unrelated to prostate cancer)	61
Death (related to prostate cancer)	2
Median age at diagnosis (years)	70 (IQR: 65–75)
Median follow-up period per patient (years)	1.9 (IQR: 1.0–3.8)
Total PSA measurements	46015
Median number of PSA measurements per patient	7 (IQR: 7–12)
Median PSA value (ng/mL)	5.6 (IQR: 4.0–7.5)
Total biopsies	11042
Median number of biopsies per patient	2 (IQR: 1–3)

2.2. Statistical Methods

The goal of the statistical analysis of the PRIAS data was to develop a model for predicting the time of disease reclassification in a personalized manner. To this end, for each patient we have the information about his age at the start of AS, all observed PSA measurements, and the time of the last negative biopsy.

We start by specifying a model which extracts the underlying $\log_2\{\text{PSA} + 1\}$ profile of each patient from the observed PSA measurements. More specifically, we specify a linear mixed effects model with $\log_2\{\text{PSA} + 1\}$ as the outcome (see Outcome–2 in Figure 3). Our model uses a separate non-linear $\log_2\{\text{PSA} + 1\}$ profile over time, for each patient. It employs patient-specific random effects to account for correlation between $\log_2\{\text{PSA} + 1\}$ measurements of the same patient. However, the PSA measurements of a patient may be higher when measured closer to the time of reclassification. This is especially an issue because PSA measurements are missing (non-random) once a patient obtains disease reclassification. The vice versa, that is, disease reclassification may be predicted by looking at the PSA is also valid. To model this two-way effect, we specify a model for time of reclassification which shares the random effects used in the model for PSA (see Figure 3). Particularly, we use a relative risk model, wherein the hazard of reclassification utilizes the shared random effects indirectly, by depending on the fitted $\log_2\{\text{PSA} + 1\}$ value and velocity (rate of change). This connected specification of a linear mixed model and relative risk model is commonly known as a joint model for time-to-event and longitudinal data [9, 10, 11].

The consequence of such a joint model is that the shared random ef-

fects represent the unobservable state of PCa of each patient. On the other hand outcomes such as disease reclassification and PSA measurements are its observable manifestations. Such a shared random effect structure allows easy addition of more disease progression indicators (e.g., MRI information) when they are available in future. Furthermore, this structure also allows the follow-up schedule for outcomes/biopsies to depend on the observed values of each other. This is especially important because yearly biopsies in the PRIAS program are scheduled on the basis of the observed PSA doubling time of a patient.

We fit the joint model using the R package **JMbayes** [**?**]. The package uses the Bayesian methodology to estimate model parameters. The model parameters and 95% credible intervals are presented in Table.. of Appendix.

2.3. Assessment of Predictions

We assessed the goodness of fit of our model using both in-sample and out-of-sample predictions. For out-of-sample predictions we utilized the XX largest AS cohorts that constitute the GAP3 database [8]. That is, we used our model to predict disease reclassification in patients of other cohorts. The accuracy of these predictions were measured via the prediction error and the area under the receiver operating characteristic curves (AUC). The prediction error represents the difference between the true disease reclassification status of a patient, and the predicted risk of reclassification. Ideally this difference should be zero. On the other hand the AUC defines if the model is able to discriminate between patients who obtain reclassification versus those do not obtain reclassification. Ideally it should be equal to one. Since we work under a longitudinal study framework we compute these measures at a gap

of every one year during the entire follow-up period.

2.4. Decision Making Framework

To assist patients and doctors in decision making for biopsies, we use the predicted risks of reclassification from our model. We calculate the probability if the patient will progress over the next ten years. We also provide an estimate of the number and time of biopsies that may be conducted, and the corresponding estimate of delay in detection of time of reclassification. Simultaneously, the patient is provided estimate of the number of time of biopsies with fixed schedule of biopsies. This allows patients to weigh harms and benefits of each strategy. We also implement this in a web-based risk calculator.

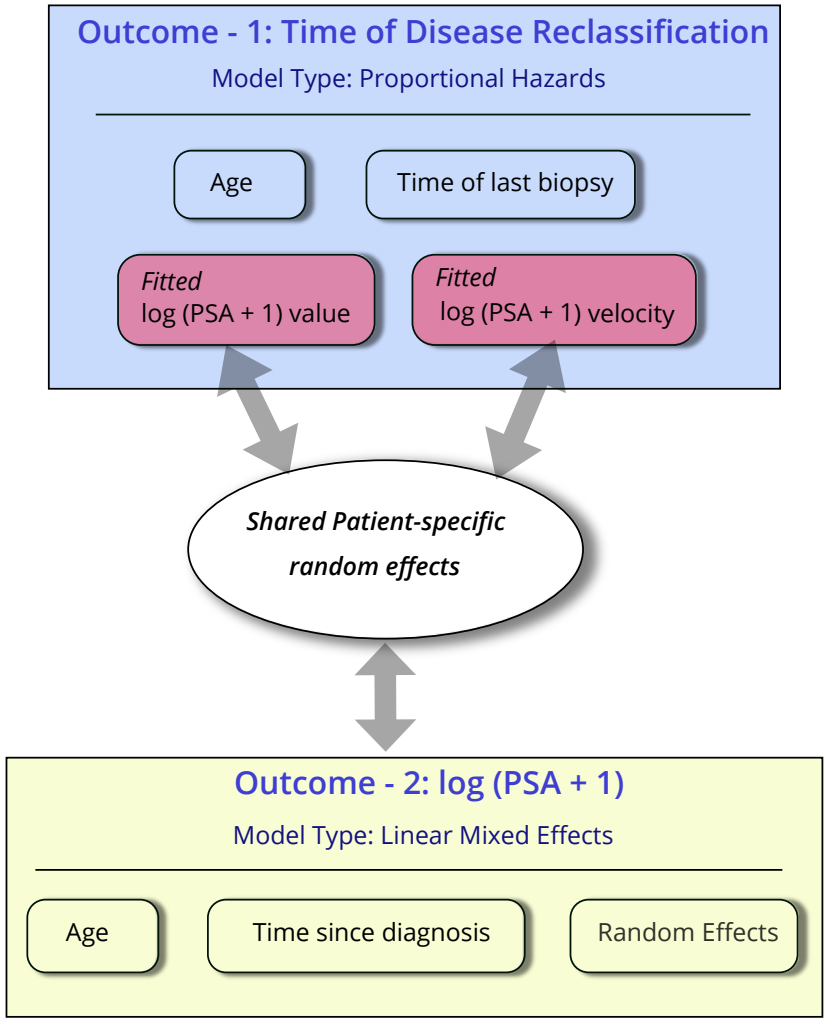

Figure 3: **Diagram of the joint model**: Per patient we observe the $\log_2\{\text{PSA} + 1\}$ transformed PSA, and the results of biopsies. We combine information from these observations to estimate the time of disease reclassification. To this end, we use a linear mixed effects model for $\log_2\{\text{PSA} + 1\}$ measurements, and proportional hazards model for time of disease reclassification. The time of disease reclassification depends on patient age, time of latest negative biopsy and underlying trend of PSA. To account for the correlation between PSA measurements and time of reclassification, the two models share patient-specific random effects in their model equations.

2.5. Model Assessment

We evaluated the accuracy of our predictios

3. Results

4. Discussion

Resources are more for only serious patients, better decisions like in the case of prostatectomy patients....so personalized approch can lead to better decisions overall as well

5. Conclusions

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Here are two sample references:.

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