Personalized Biopsies in Prostate Cancer Active Surveillance*

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Abstract

`Background`: Prostate cancer patients enrolled in active surveillance (AS) undergo repeat biopsies. When biopsy Gleason grade ≥ 2 (reclassification), treatment is commonly advised. Many patients never experience reclassification, yet undergo biopsies frequently.

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`Objective`: Better balance the number of biopsies and time delay in detection of reclassification.

`Design, Setting, and Participants`: World's largest AS study, PRIAS; 7813 patients, 1134 experienced reclassification; prostate-specific antigen (PSA) and repeat biopsy data available.

`Outcome Measurements, and Statistical Analysis`: Bayesian joint model based on accumulated clinical data used to predict patient-specific risk of reclassification. This risk was utilized to schedule personalized biopsies. Personalized and fixed schedules compared on number of biopsies and model estimated time delay in detection of reclassification for each schedule. Model validated externally in largest five AS cohorts of GAP3 database. Methodology implemented in a web-application.

`Results and Limitations`: Rate of reclassification in PRIAS was 35% at year 5 of follow-up. PSA velocity stronger predictor of reclassification (Hazard Ratio: 2.47, 95%CI: 1.93–2.99), than PSA value (Hazard Ratio: 0.99, 95%CI: 0.89–1.11). Validation: Area under ROC curve for risk predictions between 0.55 and 0.75 for PRIAS, Johns Hopkins, Toronto, and Memorial Sloan Kettering AS cohorts. Model required recalibration for all external cohorts except Johns Hopkins cohort.

`Conclusions`: We used risk predictions of reclassification to schedule personalized biopsies for AS patients. To assist patients/doctors in shared

decision making of appropriate biopsy schedule, we provided them expected time delay in detection of reclassification, for personalized/fixed schedules. Our model is externally validated, and our methodology is available for multiple AS cohorts as a web-application.

`Patient Summary`: Personalized biopsy schedules are a novel alternative to fixed biopsy schedules. They rely on patient-specific risk of reclassification and can offer better balance between number of biopsies and time delay in detection of reclassification than current schedules.
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 are usually advised active surveillance (AS) instead of immediate radical treatment [1]. In AS, cancer progression is routinely monitored via prostate-specific antigen (PSA), digital rectal examination, and repeat biopsies. Among these, the strongest indicator of cancer-related outcomes is the biopsy Gleason grade [2]. When the Gleason grade increases from grade 1 (Gleason 3+3) to 2 (Gleason 3+4) or higher, called *reclassification*, patients are commonly advised curative treatment [3].

Biopsies are conducted periodically. Consequently, reclassification is always detected with a time delay (Figure 1). For detecting reclassification timely, many AS programs schedule fixed and frequent biopsies (e.g., annually) for all patients [4, 5]. However, this also leads to many unnecessary biopsies in slow/non-progressing patients. Biopsies are invasive, painful and prone to medical complications. Thus, biopsy burden and patient non-compliance to frequent biopsies [6] has raised concerns regarding the optimal biopsy schedule [7, 8]. To this end, infrequent schedules such as biennial biopsies have been proposed as an alternative [7, 9]. Although, biennial biopsies may still lead to five unnecessary biopsies over ten years (current study period of large AS programs) for slow/non-progressing patients. A promising alternative to fixed and frequent biopsies is personalized biopsy schedules based on the patient-specific risk of reclassification (Figure 2).

The first challenge in developing personalized biopsy schedules is consolidating accumulated patient data (e.g., PSA, previous biopsy results) into risk estimates for reclassification. Existing calculators for risk of reclassifica-

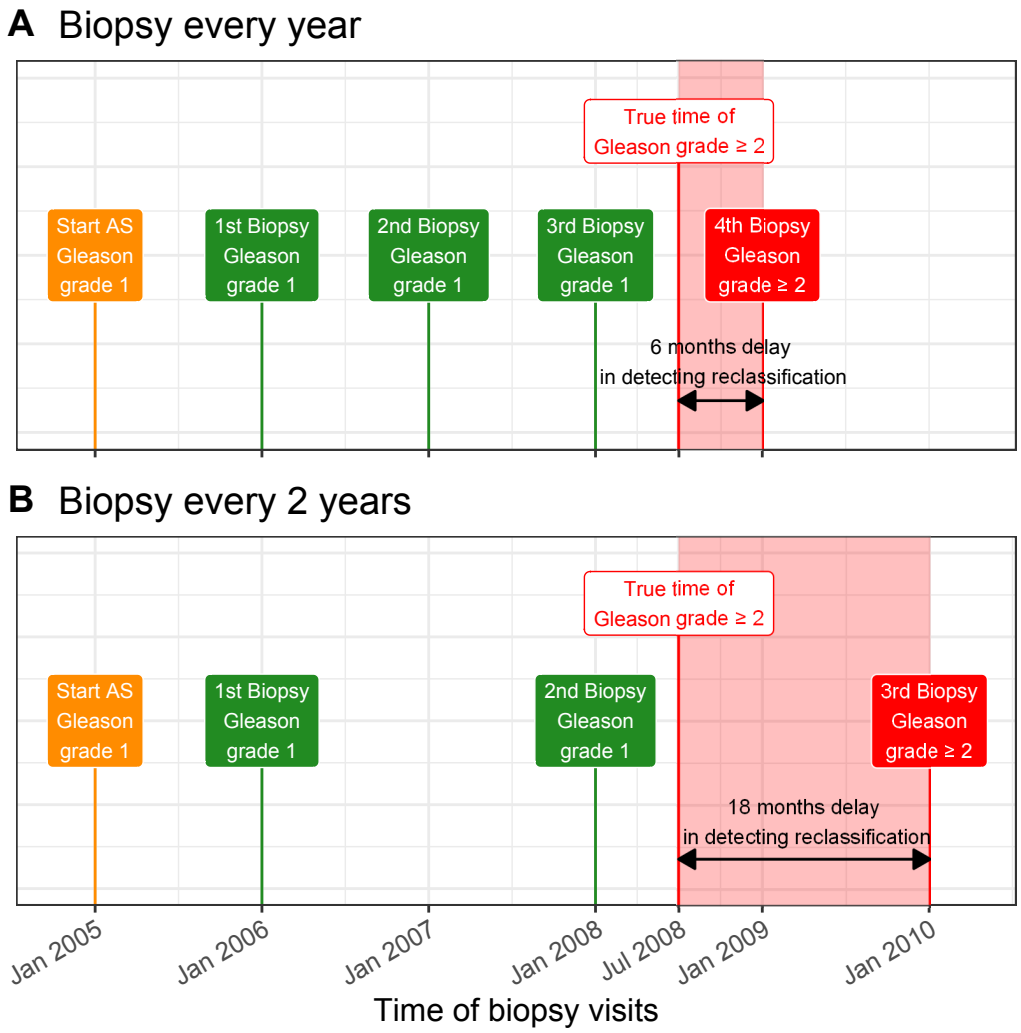

Figure 1: **Trade-off between the number of biopsies and time delay in detecting reclassification (Increase in Gleason grade from 1 to 2 or higher):** The true time of reclassification for the patient in this figure is July 2008. When biopsies are scheduled annually (**Panel A**), reclassification is detected in January 2009 with a time delay of six months, and a total of four biopsies are scheduled. When biopsies are scheduled biennially (**Panel B**) reclassification is detected in January 2010 with a time delay of 18 months, and a total of three biopsies are scheduled. Since biopsies are conducted periodically, the time of reclassification is observed as an interval. For example, between Jan 2008–Jan 2009 in **Panel A** and between Jan 2008–Jan 2010 in **Panel B**.

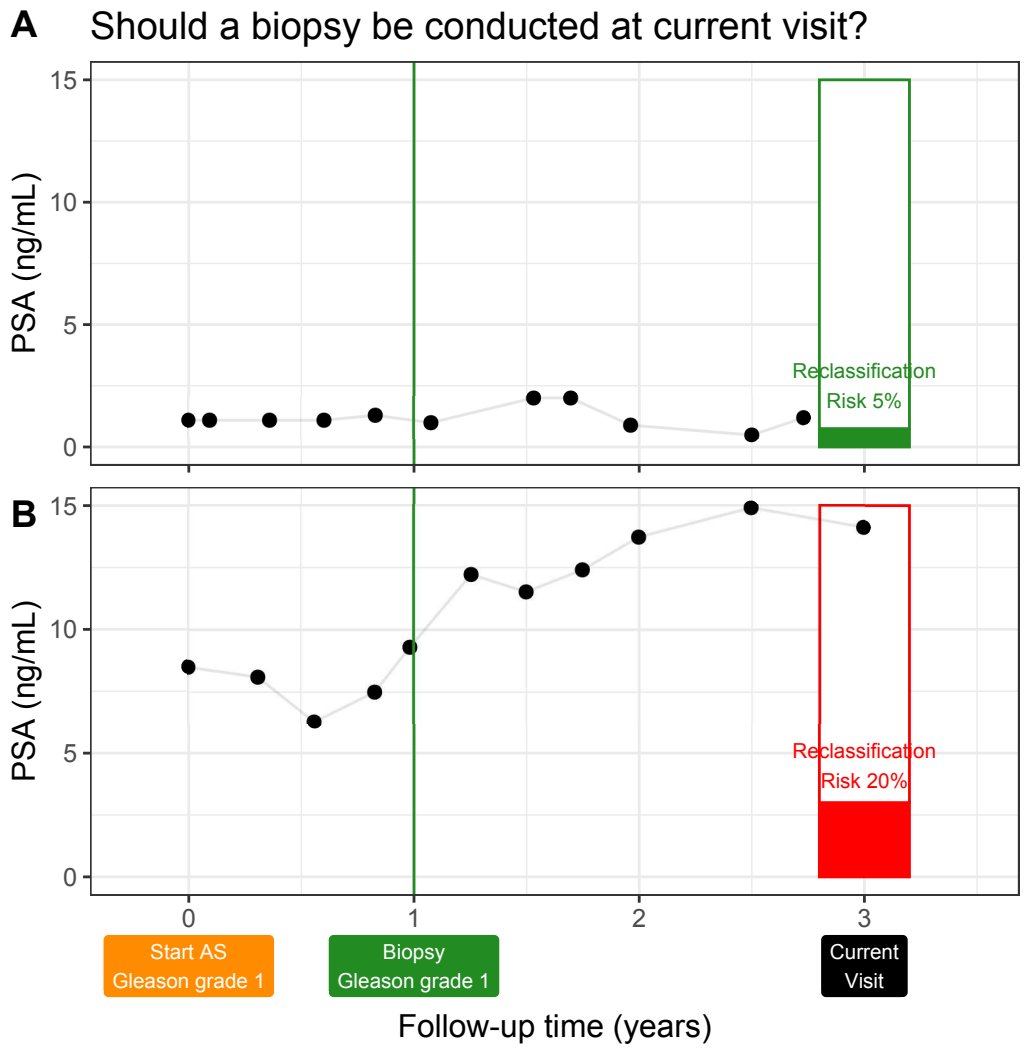

Figure 2: **Motivation for personalized risk-based decisions of biopsy**: Patient A (**Panel A**) and B (**Panel B**) had their latest biopsy at year one of follow-up (green vertical line). Patient A's prostate-specific antigen (PSA) profile remained stable until his current visit at year three, whereas patient B's profile has shown a rise. Consequently, patient B's estimated cumulative risk of reclassification at the current visit (year three) is higher than that of patient A. This makes patient B a more suitable candidate for biopsy than Patient A. Risk estimates in this figure are only illustrative.

tion [10, 11] use only the latest PSA measurement of a patient. In contrast, we intend to utilize all repeated measurements of PSA, previous biopsy results, and baseline characteristics of a patient. To this end, a suitable model is the joint model for time-to-event and longitudinal data [12, 13, 14]. A joint model predicts risk of reclassification in a personalized manner. A subsequent challenge however, is translating risks into clinical decisions. For example, a 10% risk of reclassification can be perceived high/low depending upon the patient age. Patients may also weigh risks of reclassification with the potential *consequences* of another biopsy. Two relevant *consequences* of biopsies (Figure 1) are the timing and total number of biopsies (burden), and the time delay in detecting reclassification (smaller is beneficial). The relative importance of these *consequences* can vary between the patients, and also over the follow-up period for the same patient.

The goal of this work was to assist patients and doctors in making better decisions of biopsies than fixed and frequent biopsies. For this purpose, we developed a web-application that gives patients their current and future risk of reclassification. It also suggests them risk-based personalized schedules of biopsies. For each biopsy schedule, be it fixed or personalized, the web-application provides expected *consequences* of following it. Thus, patients can compare schedules before making a decision. The web-application uses a prediction joint model fitted to the world's largest AS dataset, PRIAS [3]. We externally validated this model in largest give AS cohorts of the GAP3 database [15]. Thus, the web-application can be used by a large number of patients worldwide.

2. Patients and Methods

2.1. Study Cohort

Prostate Cancer International Active Surveillance (PRIAS) is an ongoing (December 2006 – to date) prospective cohort study of men with low- and very-low risk prostate cancer diagnoses [3]. More than 100 medical centers from 17 countries contributed to PRIAS, using a common protocol (`www.prias-project.org`). Upon inclusion in AS, PSA was measured quarterly for the first two years of follow-up and semiannually thereafter. Biopsies were scheduled at year one, four, seven, and ten of follow-up. Additional yearly biopsies were scheduled when PSA doubling time was between zero and ten years.

We selected all 7813 patients who had Gleason grade 1 [2] at the time of inclusion in PRIAS (Table 1). Our primary event of interest is increase in this Gleason grade upon repeat biopsy, called *reclassification* (1134 patients). Reclassification is a trigger for treatment advice in PRIAS. Although, 2250 patients were provided treatment on the basis of their PSA, or number of biopsy cores with cancer, or anxiety/other reasons. Our reasons for focusing solely on reclassification are, namely reclassification is strongly associated with cancer related outcomes, and other triggers for treatment vary between cohorts.

Table 1: **Summary of the PRIAS dataset**. The primary event of interest is reclassification, that is, increase in Gleason grade from grade 1 to 2 or higher. IQR: interquartile range, PSA: prostate-specific antigen.

Characteristic	**Value**
Total patients	7813
Reclassification (primary event)	1134
Treatment	2250
Watchful waiting	334
Loss to follow-up	250
Death (unrelated to prostate cancer)	95
Death (related to prostate cancer)	2
Median age at diagnosis (years)	66 (IQR: 61–71)
Median follow-up period per patient (years)	1.8 (IQR: 0.9–4.0)
Total PSA measurements	67578
Median number of PSA measurements per patient	6 (IQR: 4–12)
Median PSA value (ng/mL)	5.7 (IQR: 4.1–7.7)
Total biopsies	15686
Median number of biopsies per patient	2 (IQR: 1–2)

2.2. Statistical Model

To create personalized biopsy schedules based on patient-specific risk of reclassification, we required a risk prediction model. Available data was patient age at inclusion in AS, longitudinally measured PSA, the timing of repeat biopsies and corresponding Gleason grades, and observed time of reclassification. Analysis of this data required modeling the within-patient correlation for PSA, the association between the Gleason grades and PSA profiles of a patient, and handling missing PSA measurements when a patient experienced reclassification. In such situations, a commonly used model is the joint model for time-to-event and longitudinal data [12, 13, 14].

Our joint model consisted of two sub-models. First, a linear mixed model [16] for longitudinally measured PSA (log-transformed). Second, a relative-risk model (similar to Cox model) for obtaining the risk of reclassification. In the model for PSA, we fitted a curve to PSA measurements (Panel A, Figure 3). From each patient's fitted PSA profile we extracted the instantaneous PSA velocity. This velocity varies over time (Panel B, Figure 3). Consequently, it is more precise than the currently used constant PSA velocity assumption [17]. We connected the two sub-models by using the fitted PSA and instantaneous velocity as predictors in the sub-model for risk of reclassification (Panel C, Figure 3). Patient age was included in both sub-models. The parameters of the two sub-models were estimated jointly (Supplementary A) using the R package **JMbayes** [18].

2.3. Risk of Reclassification Based Personalized Biopsies

The key component in personalized schedules is the cumulative-risk of reclassification. Given, a patient's accumulated PSA measurements and biopsy

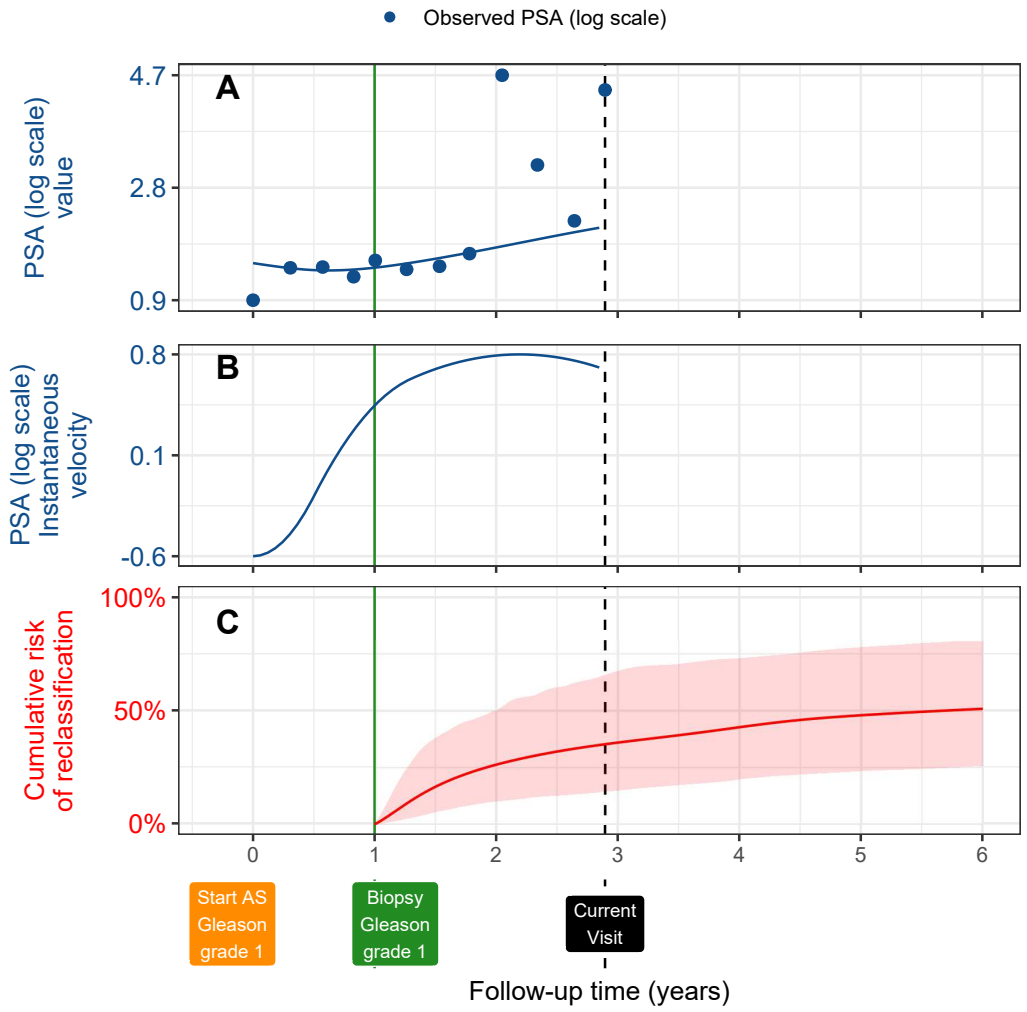

Figure 3: **Illustration of the joint model on a real PRIAS patient**. **Panel A:** Observed PSA (blue dots) and fitted PSA (solid blue line), log-transformed. **Panel B:** Estimated instantaneous velocity of PSA (log-transformed). **Panel C**: Predicted cumulative-risk of reclassification (95% credible interval shaded). Reclassification is defined as an increase in Gleason grade from grade 1 to 2 or higher. This risk of reclassification is available starting from the time of the latest negative biopsy (vertical green line at year 1 of follow-up). The joint model estimated it by combining the fitted value and estimated instantaneous velocity of PSA (log scale), and time of the latest negative biopsy. Black dashed line at year 3 denotes the time of current visit.

results, our joint model predicts the cumulative-risk of reclassification at his current as well as future visit times (Panel C, Figure 3). This cumulative-risk is also updated as more patient data becomes available over follow-up (Figure 5, Supplementary B).

In PRIAS, patient PSA is measured every 6 months. If during a PSA visit, a patient's predicted cumulative-risk of reclassification is more than a certain threshold (e.g., 10%) we schedule an immediate biopsy. Since our model predicted his cumulative-risk at his future follow-up visits as well, we can schedule future biopsies too. We achieve this by repeatedly applying the same risk threshold rule at each future follow-up visit (Supplementary C). We maintain a minimum gap of one year between consecutive biopsies (PRIAS recommendation). Example personalized schedules based on 5% and 10% risk thresholds are shown in Panel B, Figure 4.

The choice of the risk threshold in the personalized schedule dictates the *consequences* of following that schedule. *Consequences* are, the timing and the total number of biopsies, and the expected delay in detecting reclassification. Our model also estimated these *consequences* in a personalized manner (Panel B,C in Figure 4, and Figure 9–11 in Supplementary C) given any schedule of biopsies. Thus patients can compare fixed schedules with different risk personalized schedules before making a choice. Due to the limited follow-up period of PRIAS, we are only able to schedule biopsies during the first six years of follow-up of a patient (Table 12, Supplementary C).

2.4. Model Validation

We validated our model internally using the PRIAS cohort, as well as externally using largest five AS cohorts of the GAP3 database [15]. These

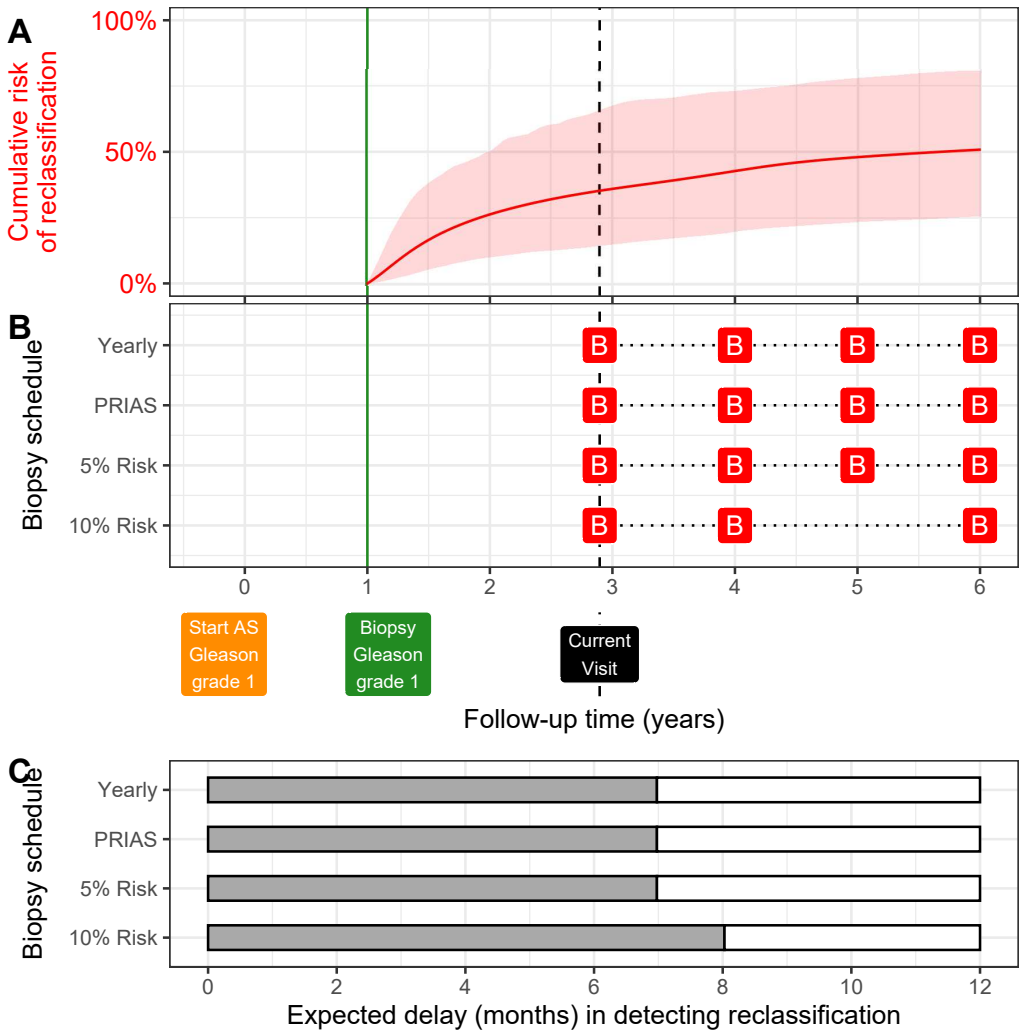

Figure 4: **Illustration of personalized and fixed schedules of biopsies**. The PSA profile of this patient is shown in Figure 3. **Panel A:** Predicted cumulative-risk of reclassification (95% credible interval shaded). **Panel B:** Personalized and fixed schedules of biopsies, with a red 'B' indicating a scheduled biopsy. **Panel C:** Expected time delay in detecting reclassification (months) for different schedules. Green vertical line at year 1 denotes the time of latest negative biopsy. Black dashed line at year 3 denotes time of current visit.

were, namely University of Toronto AS (Toronto), Johns Hopkins AS (Hopkins), Memorial Sloan Kettering Cancer Center AS (MSKCC), King's College London AS (KCL), and Michigan Urological Surgery Improvement Collaborative AS (MUSIC). We assessed our model's ability to discriminate between patients who observe reclassification versus patients who do not observe reclassification, using the area under the receiver operating characteristic curve or AUC [19]. We evaluated the prediction accuracy of our model visually using calibration plots [20, 21], and quantitatively via mean absolute prediction error [19]. Due to the longitudinal nature of AS studies, the AUC and prediction error varies over follow-up (Supplementary B.1). We recalibrated our model's baseline hazard of reclassification in those external cohorts (Supplementary B.1) where our model was miscalibrated.

2.5. Web-Application

We implemented our methodology in a web-application `https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/`. It utilizes the joint model fitted to the PRIAS dataset. Currently, the web-application supports PRIAS and the five external cohorts in which we validated our model. Patient data can be entered manually or can be uploaded in Microsoft Excel format. Predictions for risk of reclassification are shown for a limited follow-up period. This limit varies between cohorts according to their current study period (Table 12, Supplementary C). The web-application allows comparison of the *consequences* of following these schedules: personalized schedules based on 5%, 10%, and 15% risk threshold; annual biopsies; biennial biopsies; and PRIAS schedule.

3. Results

In PRIAS, the rate of reclassification within the first five years of follow-up was 35%. This rate was capped at a maximum of 50% in external GAP3 cohorts (Panel B, Figure 5). That is, many patients do not require any biopsy in the first five years.

In the fitted joint model, when patient age increased from 61 to 71 years (25-th to 75-th percentile), the adjusted hazard ratio of reclassification was 1.45 (95%CI: 1.30–1.63). When fitted PSA value (log scale) increased from 2.36 to 3.07 (25-th to 75-th percentile), the adjusted hazard ratio was 0.99 (95%CI: 0.89–1.11). When estimated instantaneous PSA (log scale) velocity increased from -0.09 to 0.31 (25-th to 75-th percentile), the adjusted hazard ratio was 2.47 (95%CI: 1.93–2.99). Hence, instantaneous velocity of PSA (log scale) was a stronger predictor for reclassification than its value. Detailed parameter estimates are in Supplementary A.2.

The time-varying AUC and calibration of our model in different cohorts are shown in Panel A and Panel B of Figure 5, respectively. The AUC achieves a moderate level in all cohorts. It fluctuates roughly around 0.63 over time. In terms of calibration, our model seems well calibrated only for the Johns Hopkins AS cohort. However, we resolved this issue by recalibrating the baseline hazard of our model separately for each cohort (Figure 6, Supplementary B). The resulting risk predictions for individual patients from this recalibrated model and from separately fitted new joint models for each cohort were similar (Figure 7, Supplementary B). Comprehensive discussion of validation results is in Supplementary B.

Various personalized and fixed biopsy schedules for a demonstration pa-

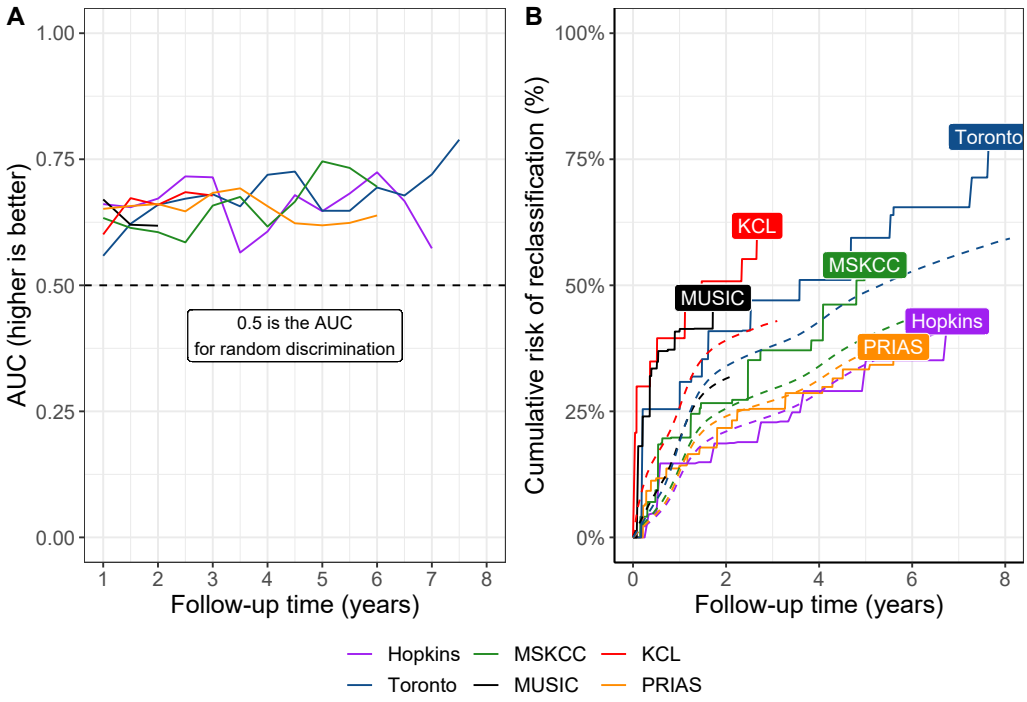

Figure 5: **Model Validation Results**. **Panel A**: time dependent area under the receiver operating characteristic curve or AUC (measure of discrimination). **Panel B**: calibration-at-large [20, 21], with solid lines depicting the non-parameteric estimate of the cumulative-risk of reclassification [22], and dashed lines showing the average cumulative-risk of reclassification obtained using the joint model fitted to the PRIAS dataset. Full names of Cohorts are *PRIAS*: Prostate Cancer International Active Surveillance, *Toronto*: University of Toronto Active Surveillance, *Hopkins*: Johns Hopkins Active Surveillance, *MSKCC*: Memorial Sloan Kettering Cancer Center Active Surveillance, *KCL*: King's College London Active Surveillance, *MUSIC*: Michigan Urological Surgery Improvement Collaborative Active Surveillance.

tient in Figure 4 show that a personalized schedule based on 10% risk threshold leads to one less biopsy than other schedules. At the same time, the corresponding time delay in detection of reclassification is expected to be only one month more than other schedules. A compulsory biopsy was scheduled at year six (maximum biopsy scheduling time of our model, Supplementary C) in all schedules for a meaningful comparison across schedules. Schedules for other demonstration patients are in Figure 9–11, Supplementary C.

4. Discussion

We developed a novel methodology and statistical model for personalized biopsy schedules in prostate cancer active surveillance (AS) patients. Personalized schedules utilize patient-specific risks of reclassification. Reclassification is defined as increase in Gleason grade [2] from grade 1 to 2 or higher upon repeat biopsy. Reclassification risk calculators are not new [13, 23]. However, our work has four novel features. First, we developed a statistical model for developing personalized schedules using the world's largest AS cohort PRIAS. Second, we created a methodology to estimate time delay in detection of reclassification (less is beneficial) in a personalized manner, given any biopsy schedule. Thus patients/doctors can compare schedules before making a choice. Third, we externally validated our model in the largest five AS cohorts of the GAP3 database [15]. Fourth, we implemented our methodology in a web-application `https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/` for PRIAS and externally validated cohorts.

Currently, in AS, either fixed schedules are used (e.g., annual biopsies), or PSA is used to trigger biopsies. Both approaches have been criticized [17, 6]. We argue that current approaches have not exploited PSA fully and correctly. For example, using observed PSA is incorrect as it has measurement error. Other approaches utilize only the latest PSA and/or when they utilize all PSA data they assume it changes over time linearly (constant PSA velocity). In contrast, our joint model builds a measurement error free patient-specific profile of PSA using all PSA measurements. It allows PSA to increase/decrease non-linearly over time (non-constant PSA velocity). Sub-

sequently, it consolidates underlying PSA value and velocity, previous biopsy results, and baseline characteristics of a patient, to yield a single personalized estimate for the risk of reclassification. Furthermore, this risk gets updated as more patient data becomes available over follow-up. This is a more holistic approach. Although we have not incorporated newer biomarkers and magnetic resonance imaging (MRI) data, when this information becomes available we can add them as predictors in our model. Decisions based on combined information from multiple sources can yield better results than based on MRI or PSA alone.

Our model is useful for a large number of patients from PRIAS, as well as from the largest five AS cohorts of the GAP3 database in which we validated our model. These are the University of Toronto AS, Johns Hopkins AS, Memorial Sloan Kettering Cancer Center AS, King's College London AS, and Michigan Urological Surgery Improvement Collaborative AS. We required recalibration of our model's baseline hazard of reclassification for all of these cohorts except the Johns Hopkins cohort. This can be explained by the fact that both PIRAS and Johns Hopkins cohorts have the same marginal rate of reclassification over time (Panel B, Figure 5). Extending our model in smaller cohorts requires only recalibrating our model.

Our work has important clinical implications. The rate of reclassification after five years of follow-up was capped at 50% in all cohorts that we evaluated (Figure 5). That is, a large number of patients do not require any biopsy during the first five years of follow-up. Given the non-compliance and burden of frequent biopsies [6], the availability of our methodology as a web-application may encourage patients/doctors to consider personalized sched-

ules instead. To assist them in this decision making, the web-application provides an estimate of time delay in detection of reclassification for both personalized and fixed schedules, in a personalized manner. We hope this will objectively address patient apprehensions regarding adverse outcomes in AS.

This work has certain limitations. The proposed model is valid only for the first six years of follow-up in PRIAS, whereas reclassification may occur much later in many patients. This problem can be mitigated by refitting the model with new follow-up data in the future. While we focused only on reclassification, the number of positive biopsy cores can also be used to trigger treatment. We did not consider such additional criteria because they differ between cohorts [4], whereas, reclassification is commonly used. Although, reclassification is susceptible to inter-observer variation. Models which account for this variation [13, 24] will be interesting to investigate further. However, the methodology for personalized scheduling, and for comparison of various schedules need not change.

5. Conclusions

We developed a novel methodology and statistical model for personalized scheduling of biopsies in prostate cancer active surveillance (AS) patients. Unlike fixed biopsy schedules, personalized schedules utilize a patient's risk of reclassification to decide biopsies. They also update as more patient data becomes available over follow-up. Our model is externally validated in largest five AS cohorts of the GAP3 database. Our methodology is implemented in a web-application (`https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/`) and is accessible to large number of AS patients from the validated cohorts. To assist patients/doctors in making a shared decision of an appropriate biopsy schedule, the web-application provides expected time delay in detection of reclassification (smaller is beneficial), and timing and total number of biopsies (burden), for both personalized and currently used fixed schedules.

Author Contributions

Anirudh Tomer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tomer, Nieboer, Roobol, Bjartell, and Rizopoulos

Acquisition of data: Tomer, Nieboer, and Roobol

Analysis and interpretation of data: Tomer, Nieboer, and Rizopoulos

Drafting of the manuscript: Tomer, and Rizopoulos

Critical revision of the manuscript for important intellectual content: Tomer, Nieboer, Roobol, Bjartell, Steyerberg, and Rizopoulos

Statistical analyses: Tomer, Nieboer, Steyerberg, and Rizopoulos

Obtaining funding: Roobol, and Rizopoulos

Administrative, technical or material support: Nieboer

Supervision: Roobol, and Rizopoulos

Other: none

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