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 [10, 11, 12]. 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.

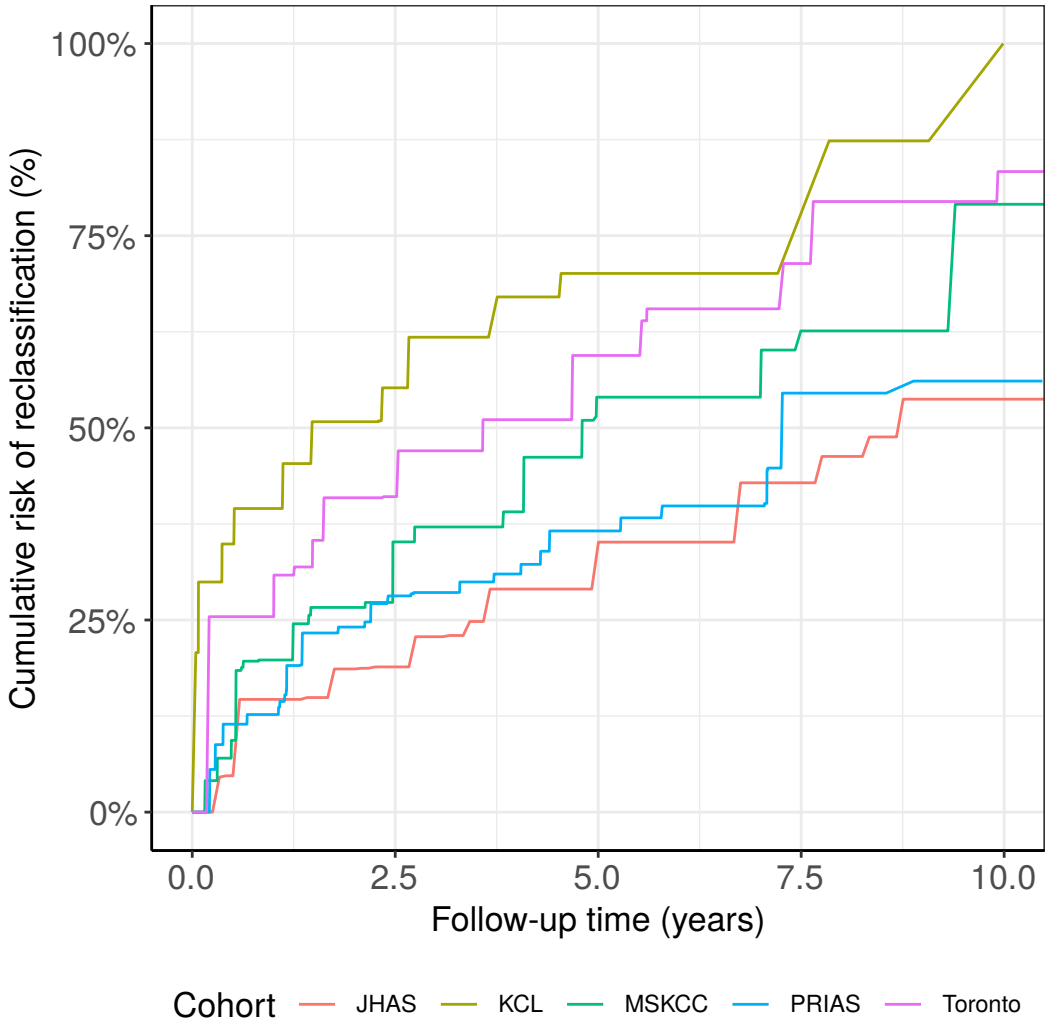

Figure 1: **Active Surveillance Cancer Patients Are Often *Slowly Progressing*.** Graph shows estimated cumulative risk of reclassification[2] in AS in five of the largest AS studies that are part of the GAP3 database [8]. In all cohorts except KCL, roughly 50% patients do not require any biopsy in first 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

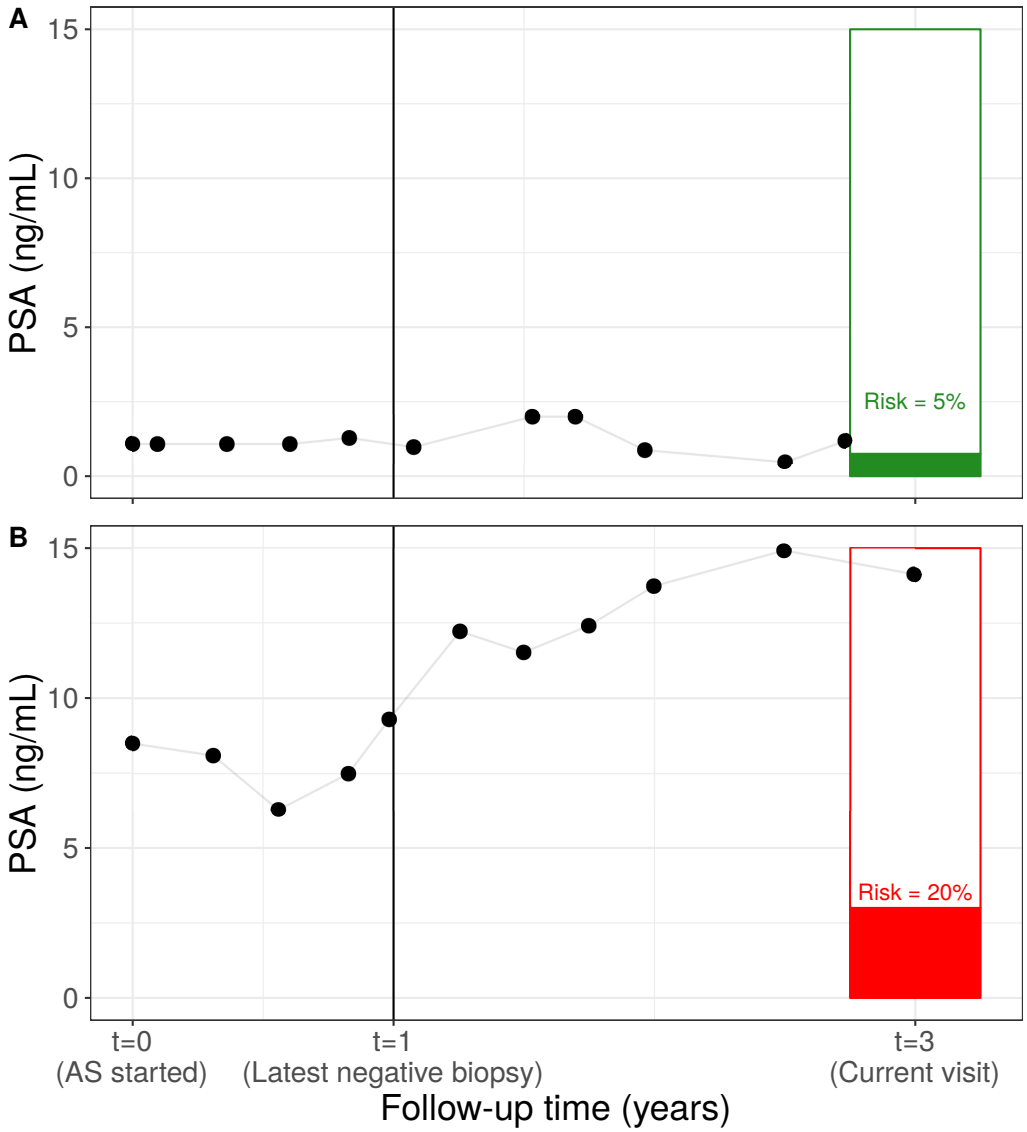

Figure 2: **Motivation for risk based decisions of biopsy**: Patient A and B had their latest biopsy at year one of follow-up. Patient A's prostate-specific antigen (PSA) profile remained stable until the current visit time at year three. Consequently, his cumulative risk of reclassification at year 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%. A biopsy may be recommended for patient B 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 disease reclassification. The PRIAS dataset has certain features which need to be accounted for in the modeling process. For example, the PSA measurements for each patient are more similar/correlated than with other patients. The PSA profiles of patients are also non-linear. While compliance to PSA measurements is high (90%), PSA measurements of patients who obtain disease reclassification are not available after reclassification. These missing observations if were available were likely going to be higher than the measurements of patients who did not obtain Gleason reclassification.

2.3. 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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