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Original Article

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Personalised biopsy schedules based on risk of Gleason upgrading for patients with low-risk prostate cancer on active surveillance

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Objective

To develop a model and methodology for predicting the risk of Gleason upgrading in patients with prostate cancer on active surveillance (AS) and using the predicted risks to create risk-based personalised biopsy schedules as an alternative to one-size-fits-all schedules (e.g. annually). Furthermore, to assist patients and doctors in making shared decisions on biopsy schedules, by providing them quantitative estimates of the burden and benefit of opting for personalised vs any other schedule in AS. Lastly, to externally validate our model and implement it along with personalised schedules in a ready to use web-application.

Patients and Methods

Repeat prostate-specific antigen (PSA) measurements, timing and results of previous biopsies, and age at baseline from the world's largest AS study, Prostate Cancer Research International Active Surveillance (PRIAS; 7813 patients, 1134 experienced upgrading). We fitted a Bayesian joint model for time-to-event and longitudinal data to this dataset. We then validated our model externally in the largest six AS cohorts of the Movember Foundation's third Global Action Plan (GAP3) database (>20 000 patients, 27 centres worldwide). Using the model predicted upgrading risks; we scheduled biopsies whenever a patient's upgrading risk was above a certain threshold. To assist patients/doctors in the choice of this threshold, and to compare the resulting personalised schedule with currently practiced schedules, along with the timing and the total number of biopsies (burden) planned, for each schedule we provided them with the time delay expected in detecting upgrading (shorter is better).

Results

The cause-specific cumulative upgrading risk at the 5-year follow-up was 35% in PRIAS, and at most 50% in the GAP3 cohorts. In the PRIAS-based model, PSA velocity was a stronger predictor of upgrading (hazard ratio [HR] 2.47, 95% confidence interval [CI] 1.93–2.99) than the PSA level (HR 0.99, 95% CI 0.89–1.11). Our model had a moderate area under the receiver operating characteristic curve (0.6–0.7) in the validation cohorts. The prediction error was moderate (0.1–0.2) in theGAP3 cohorts where the impact of the PSA level and velocity on upgrading risk was similar to PRIAS, but large (0.2–0.3) otherwise. Our model required re-calibration of baseline upgrading risk in the validation cohorts. We implemented the validated models and the methodology for personalised schedules in a web-application (http://tiny.cc/biopsy).

Conclusions

We successfully developed and validated a model for predicting upgrading risk, and providing risk-based personalised biopsy decisions in AS of prostate cancer. Personalised prostate biopsies are a novel alternative to fixed one-size-fits-all schedules, which may help to reduce unnecessary prostate biopsies, while maintaining cancer control. The model and schedules made available via a web-application enable shared decision-making on biopsy schedules by comparing fixed and personalised schedules on total biopsies and expected time delay in detecting upgrading.

Keywords
active surveillance, biopsies, personalised medicine, prostate cancer, shared decision-making

Introduction

Patients with low- and very-low-risk screening-detected localised prostate cancer are usually recommended for active surveillance (AS), instead of immediate radical treatment [1]. In AS, cancer progression is monitored routinely via PSA measurement, DRE, repeat biopsies, and recently, MRI. Among these, the strongest indicator of cancer-related outcomes is the biopsy Gleason Grade Group (GGG) [2]. When it increases from GGG1 (Gleason 3 + 3) to GGG2 (Gleason 3 + 4) or higher, it is called 'upgrading' [3]. Upgrading is an important endpoint in AS upon which patients' are commonly advised curative treatments [4].

Biopsies in AS are always conducted with a time gap between them. Consequently, upgrading is always detected with a time delay (Fig. 1) that cannot be measured directly. In this regard, to detect upgrading in a timely manner, many patients are prescribed fixed and frequent biopsies, most often annually [5]. However, such one-size-fits-all schedules lead to unnecessary biopsies in slow/non-progressing patients. Biopsies are invasive, may be painful, and are prone to medical complications such as bleeding and septicaemia [6]. Thus, biopsy burden and patient non-compliance to frequent biopsies [7] have raised concerns regarding the optimal biopsy schedule [8,9] in AS.

Except for the confirmatory biopsy at 1 year of AS [7], opinions and practice regarding the timing of remaining biopsies lack consensus [10]. Some AS programmes utilise patients' observed PSA level, DRE, previous biopsy Gleason Grade, and lately, MRI results to decide whether to take biopsies [4,10,11]. In contrast, others discourage schedules based on clinical data and MRI results [5,12], and instead support periodical one-size-fits-all biopsy schedules. Furthermore, some suggest replacing frequent periodical schedules with infrequent ones (e.g. biennially) [8,13]. Each of these approaches has limitations. For example, one-size-fits-all schedules can lead to many unnecessary biopsies because of differences in baseline upgrading risk across cohorts [8]. Whereas, as observed clinical data have measurement error (e.g. PSA fluctuations) a flaw in using it directly is that it may lead to poor decisions. Also, decisions based on clinical data typically rely only on the latest data point and ignore previous repeated measurements. A novel alternative that counters these drawbacks is first processing patient data via a statistical model, and subsequently using model-predicted upgrading risks to create personalised biopsy schedules [10] (Fig. 2). While, upgrading-risk calculators are not new [14,15–17], not all are personalised either. Besides, they do not specify how risk predictions can be exploited to create a schedule.

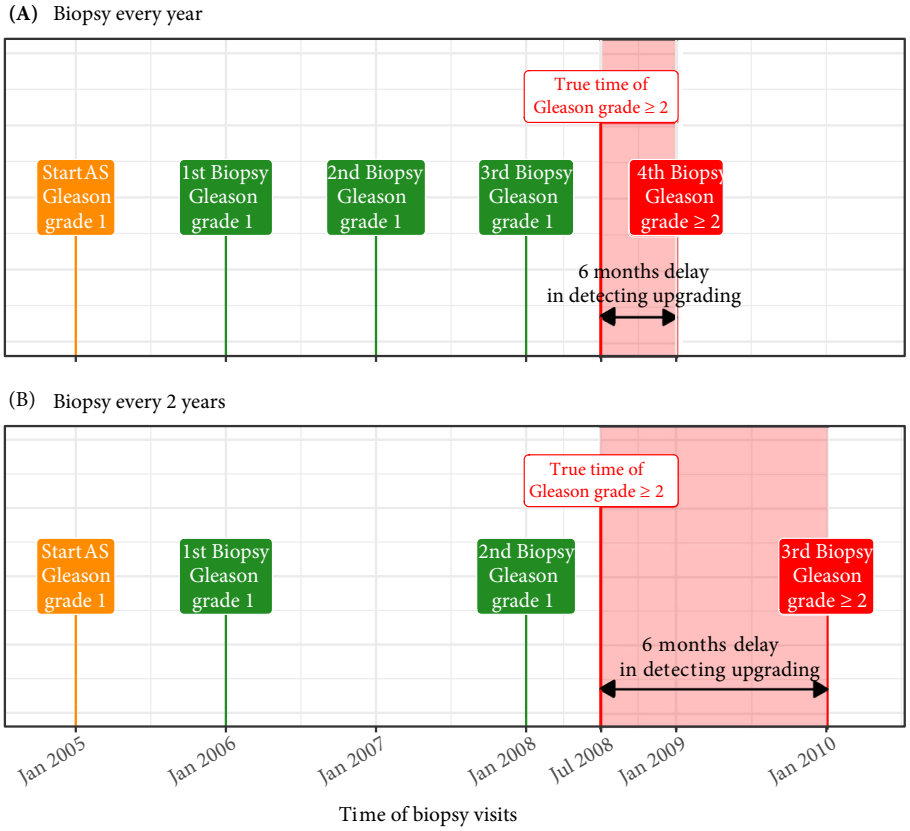
The present work was motivated by the problem of scheduling biopsies in AS. We had two goals. First, we wanted to assist practitioners in using clinical data in biopsy decisions in a statistically sound manner. To this end, we planned to develop a robust, generalisable statistical model that provides reliable individual upgrading risk in AS. Subsequently, we would employ these predictions to derive risk-based personalised biopsy schedules. Our second goal was to enable shared decision-making on biopsy schedules. We intended to achieve this by allowing patients and doctors to compare the burden and benefit (Fig. 1) of opting for personalised schedules vs periodical schedules vs schedules based on clinical data. Specifically, we proposed timing and number of planned biopsies (more/frequent are burdensome), and the expected time delay in detecting upgrading (shorter is beneficial) for any given schedule. While fulfilling our goals, we wanted to capture the maximum possible information from the available data. Hence, we used all repeated PSA measurements of patients, previous biopsy results, and baseline characteristics. To fit this model, we utilised data of the world's largest AS study, Prostate Cancer Research International Active Surveillance (PRIAS). To evaluate our model, we externally validated it in the largest six AS cohorts from the Movember Foundation's third Global Action Plan (GAP3) database [18]. Last, we aimed to implement the validated model and methodology in a web-application.

Patients and Methods

Study Cohort

For developing a statistical model to predict upgrading risk, we used the world's largest AS dataset, PRIAS [4], dated April 2019 (Table 1). In PRIAS, biopsies were scheduled at 1, 4, 7, and 10 years, and additional yearly biopsies were scheduled when PSA doubling time was between zero and 10 years. We selected all 7813 patients who had GGG1 at inclusion in AS. Our primary event of interest was an increase in this GGG observed upon repeat biopsy, called 'upgrading' (1134 patients). Upgrading is a trigger for treatment advice in PRIAS. Some examples of treatment

Fig. 1 Trade-off between the timing and number of biopsies (burden) and time delay in detecting Gleason upgrading (shorter is better): the true time of Gleason upgrading (increase in GGG1 to GGG≥2) for the patient in this figure is July 2008. When biopsies are scheduled annually (Panel **A**), upgrading is detected in January 2009 with a time delay of 6 months, and a total of four biopsies are scheduled. When biopsies are scheduled biennially (Panel **B**), upgrading is detected in January 2010 with a time delay of 18 months, and a total of three biopsies are scheduled. As biopsies are conducted periodically, the time of upgrading is observed as an interval. For example, between January 2008 and January 2009 in Panel **A** and between January 2008 and January 2010 in Panel **B**. The phrase 'Gleason Grade Group' is shortened to 'Gleason grade' for brevity.



options in AS are radical prostatectomy, brachytherapy, definitive radiation therapy, and other alternative local treatments such as cryosurgery, high-intensity focussed ultrasound, and external beam radiation therapy. Comprehensive details on treatment options and their side-effects are available in European Association of Urology (EAU)-European Society for Radiotherapy and Oncology (ESTRO)-International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer [19]. In PRIAS, 2250 patients were provided treatment based on their PSA level, the number of biopsy cores with cancer, or anxiety/other reasons. However, our reason for focussing solely on upgrading was that upgrading is strongly associated with cancer-related outcomes, and other treatment triggers vary between cohorts [10].

For externally validating our model's predictions, we selected the following largest (by the number of repeated measurements) six cohorts from Movember Foundation's GAP3 database [18], version 3.1, covering nearly 73% of the GAP3 patients: the University of Toronto AS (Toronto), Johns Hopkins AS (Hopkins), Memorial Sloan Kettering Cancer Center AS (MSKCC), King's College London AS (KCL), Michigan Urological Surgery Improvement Collaborative AS (MUSIC), and University of California San Francisco AS (UCSF, version 3.2). Only patients with a GGG1 at the time of inclusion in these cohorts were selected. Summary statistics are presented in Appendix S1.2.

Choice of Predictors

In our model, we used all repeated PSA measurements, the timing of the previous biopsy and Gleason Grade, and age at inclusion in AS. Other predictors, e.g. prostate volume and MRI results, can also be important. MRI is utilised already for targeting biopsies, but regarding its use in deciding the time of biopsies, there are arguments both for and against it [11,12,20]. MRI is still a recent addition in most AS

Fig. 2 Motivation for upgrading risk based personalised biopsy decisions: to utilise patients' complete longitudinal data and results from previous biopsies in making biopsy decisions. For this purpose, we first process data using a statistical model and then utilise the patient-specific predictions for risk of Gleason upgrading to schedule biopsies. For example, Patient A (Panel **A**) and B (Panel **B**) had their latest biopsy at 1 year of follow-up (green vertical line). Patient A's PSA profile remained stable until his current visit at 2 years, whereas patient B's profile has shown a rise. Consequently, patient B's upgrading risk at the current visit (2 years) 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.

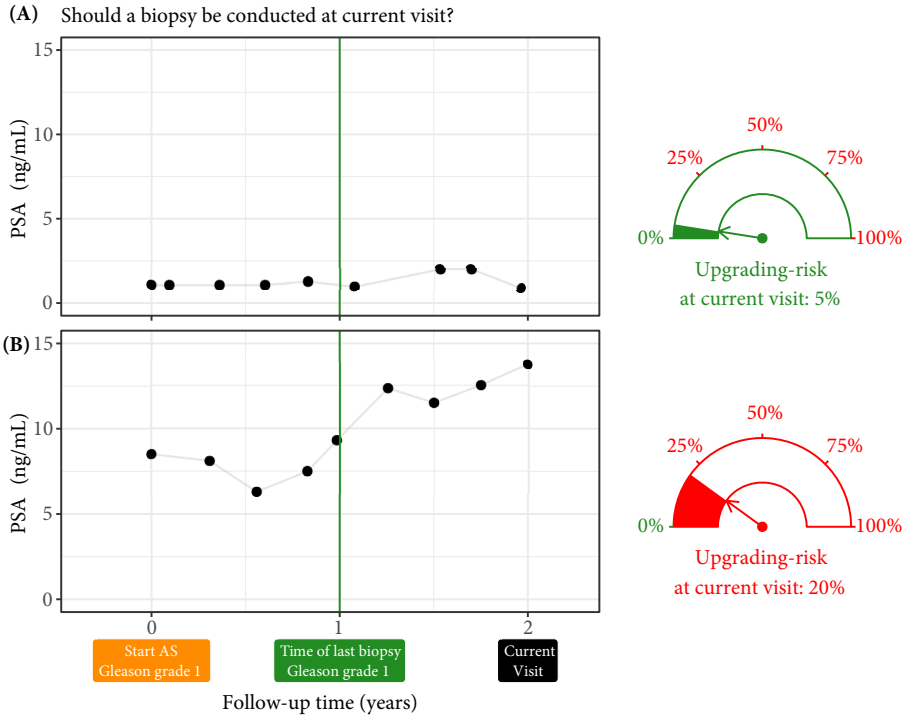


Table 1 Summary of the PRIAS dataset as of April 2019.

Characteristic	Value
Total patients, *n*	7813
Upgrading (primary event), *n*	1134
Treatment, *n*	2250
Watchful waiting, *n*	334
Loss to follow-up, *n*	249
Death (unrelated to prostate cancer), *n*	95
Death (related to prostate cancer), *n*	2
Age at diagnosis, years, median (IQR)	66 (61–71)
Maximum follow-up per patient, years, median (IQR)	1.8 (0.9–4.0)
Total PSA measurements, *n*	67 578
Number of PSA measurements per patient, median (IQR)	6 (4–12)
PSA level, ng/mL, median (IQR)	5.7 (4.1–7.7)
Total biopsies, *n*	15 686
Number of biopsies per patient, median (IQR)	2 (1–2)

IQR, interquartile range. The primary event of interest is upgrading, that is, increase from GGG1 to GGG≥2 [2]. Study protocol URL: https://www.prias-project.org.

protocols. Consequently, repeated MRI data were very sparsely available in both PRIAS and GAP3 databases to make a stable prediction model. Prostate volume data was also sparsely available, especially in the validation cohorts. Based on these reasons, we did not include them in our model.

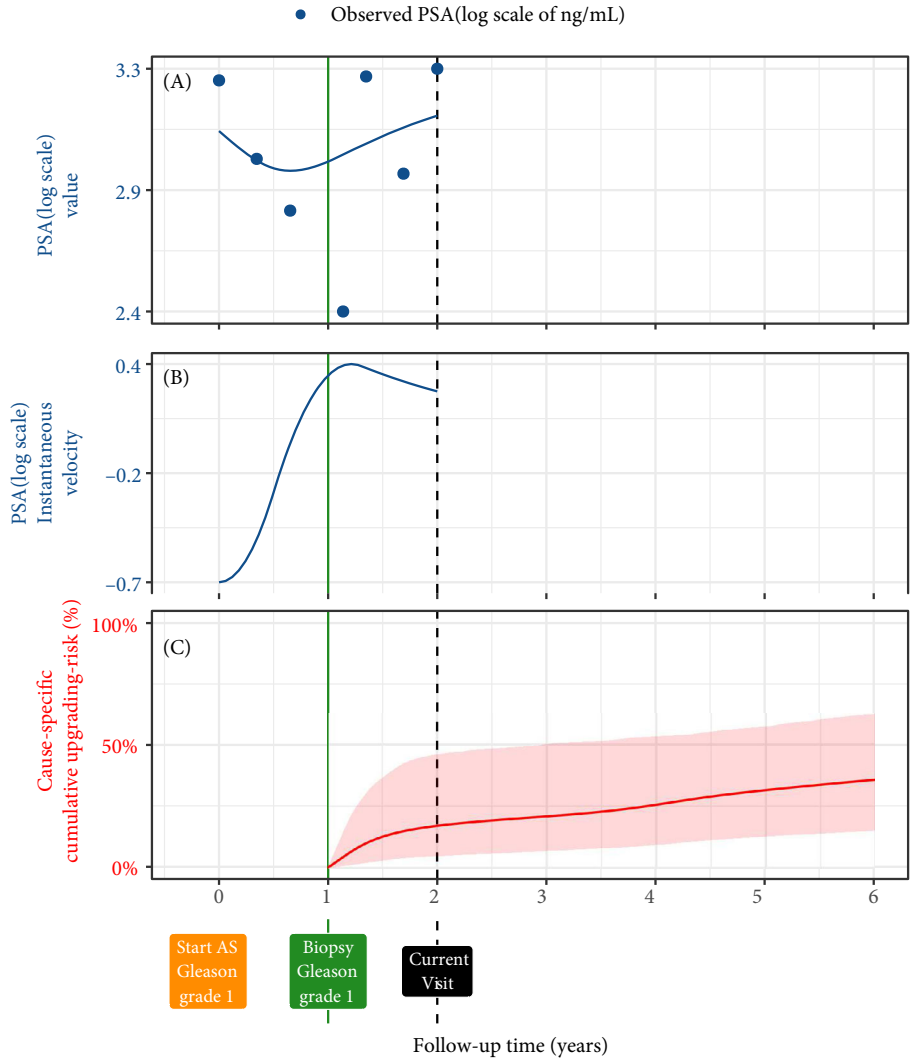
Statistical Model

Modelling an AS dataset such as PRIAS, posed certain challenges. First, PSA level was measured longitudinally, and over follow-up time it did not always increase linearly. Consequently, we expect that PSA measurements of a patient are more similar to each other than of another patient. In other words, we needed to accommodate the within-patient correlation for PSA level. Second, the PSA level was available only until a patient observed upgrading. Thus, we also needed to model the association between the Gleason Grades and PSA profiles of a patient, and handle missing PSA measurements after a patient had upgrading. Third, as the PRIAS biopsy schedule uses PSA, a patient's observed time of upgrading was also dependent on their PSA. Thus, the effect of PSA on the upgrading risk needed to be adjusted for the effect of PSA on the biopsy schedule. Fourth, many patients obtained treatment and watchful waiting before observing upgrading. As we considered events other than upgrading as censoring, the model needed to account for patients' reasons for treatment or watchful waiting (e.g. age, treatment based on observed data). A model that handles these challenges in a statistically sound manner is the joint model for time-to-event and longitudinal data [14,21,22].

Our joint model consisted of two sub-models; namely, a linear mixed-effects sub-model [23] for longitudinally measured PSA (log-transformed) and a relative-risk sub-model (similar to the Cox model) for the interval-censored time of upgrading. Patient age was used in both sub-models. Results and timing of the previous negative biopsies were used only in the risk sub-model. To account for PSA fluctuations [24], we assumed *t*-distributed PSA measurement errors. The correlation between PSA measurements of the same patient was established using patient-specific random-effects. We fitted a unique curve to the PSA measurements of each patient (Panel A, Fig. 3 [2]). Subsequently, we calculated the mathematical derivative of the patient's fitted PSA profile (Appendix S1, Equation 2), to obtain his follow-up time-specific instantaneous PSA velocity (Panel B, Fig. 3). This instantaneous velocity is a stronger predictor of upgrading than the widely used average PSA velocity [25].

We modelled the impact of PSA on upgrading risk by employing fitted PSA level and instantaneous velocity as predictors in the risk sub-model (Panel C, Fig. 3). We adjusted the effect of PSA on upgrading risk for the PSA-dependent PRIAS biopsy schedule by estimating parameters using a full likelihood method (proof in Appendix S1). This approach also accommodates watchful waiting and treatment protocols that are also based on patient data. Specifically, the

Fig. 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 from ng/mL. Panel **B**: Estimated instantaneous velocity of PSA (log-transformed). Panel **C**: Predicted cause-specific cumulative upgrading risk (95% credible interval shaded). Upgrading is defined as an increase in the GGG1 to GGG≥2 [2]. This upgrading risk is calculated starting from the time of the latest negative biopsy (vertical green line at 1 year of follow-up). The joint model estimated it by combining the fitted PSA (log scale) level and instantaneous velocity, and time of the latest negative biopsy. Black dashed line at 2 years denotes the time of current visit.



parameters of our two sub-models were estimated jointly under the Bayesian paradigm (Appendix S1) using the R package JMbayes [26].

Risk Prediction and Model Validation

Our model provides predictions for upgrading risk over the entire future follow-up period of a patient (Panel C, Fig. 3). However, we recommend using predictions only after 1 year. This is because most AS programmes recommend a confirmatory biopsy at 1 year, especially to detect patients who may be misdiagnosed as low grade at inclusion in AS. The risk predictions for a patient are not calculated only once. Rather, as illustrated in Fig. S5 of Appendix S2, risk-predictions update over the follow-up, to account for additional patient data (e.g. new biopsy results, PSA measurements) that become available. We validated our model internally in the PRIAS cohort, and externally in the largest six GAP3 database cohorts. We employed calibration plots [27,28] and follow-up time-dependent mean absolute risk prediction error (MAPE) [29] to graphically and quantitatively evaluate our model's risk prediction accuracy, respectively. We assessed our model's ability to discriminate between patients who experience/do not experience upgrading via the time-dependent area under the receiver operating characteristic curve (AUC) [29].

The aforementioned time-dependent AUC and MAPE [29] are temporal extensions of their standard versions [28] in a longitudinal setting. Specifically, at every 6 months of follow-up, we calculated a unique AUC and MAPE for predicting upgrading risk in the subsequent 1 year (Appendix S2.1). For emulating a realistic situation, we calculated the AUC and MAPE at each follow-up using only the validation data available until that follow-up. For example, calculations for AUC and MAPE for the time interval 2–3 years do not utilise data of patients who progressed before 2 years. Last, to resolve any potential model miscalibration in the validation cohorts, we aimed to re-calibrate our model's baseline hazard of upgrading (Appendix S2.1), individually for each cohort.

Results

The cause-specific cumulative upgrading risk at the 5-year follow-up was 35% in PRIAS and at most 50% in the validation cohorts (Panel B, Fig. 4). In the fitted PRIAS model, the adjusted hazard ratio (aHR) of upgrading for an increase in patient age from 61 to 71 years (25th to 75th percentile) was 1.45 (95% CI 1.30–1.63). For an increase in fitted PSA level from 2.36 to 3.07 ng/mL (25th to 75th percentile, log scale), the aHR was 0.99 (95% CI 0.89–1.11). The strongest predictor of upgrading risk was instantaneous PSA velocity, with an increase from −0.09 to 0.31 (25th to 75th percentile), giving an aHR of 2.47 (95% CI 1.93–2.99). The aHR for PSA level and velocity was different in each GAP3 cohort (Appendix S1.3: Table S8).

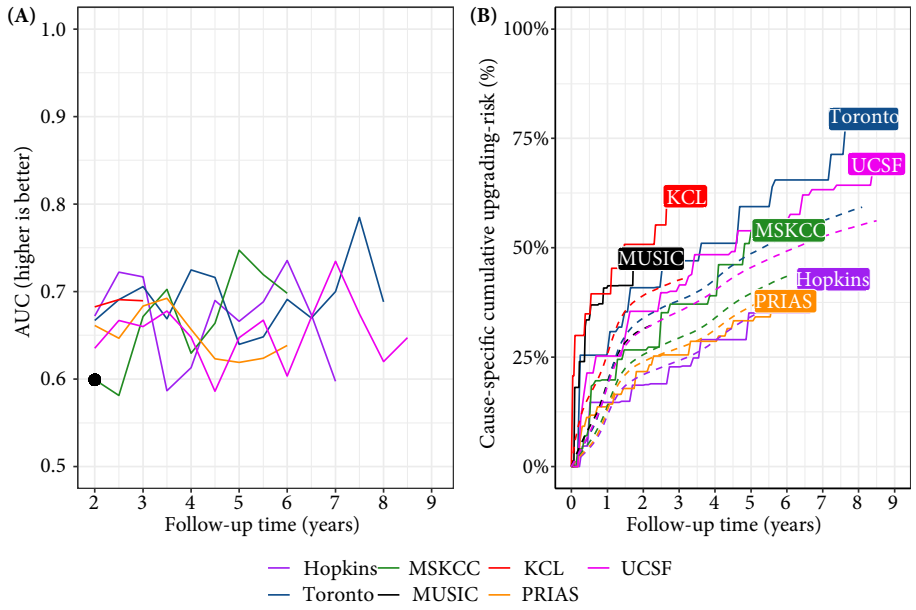
The time-dependent AUC, calibration plot, and time-dependent MAPE of our model are shown in Fig. 4, and Appendix S2.1: Fig. S8. In all cohorts, time-dependent AUC was moderate (0.6–0.7) over the whole follow-up period. Time-dependent MAPE was moderate (0.1–0.2) in those cohorts where the impact of PSA on upgrading risk was similar to PRIAS (e.g. Hopkins cohort, Appendix S1.3: Table S8), and large (0.2–0.3) otherwise. Our model was miscalibrated for the validation cohorts (Panel B, Fig. 4) because cohorts had differences in inclusion criteria (e.g. PSA density) and follow-up protocols [18], which were not accounted for in our model. Consequently, the PRIAS-based model's fitted baseline hazard did not correspond to the baseline hazard in the validation cohorts. To solve this problem, we re-calibrated the baseline hazard of upgrading in the validation cohorts (Appendix S2.1: Fig. S6). We compared risk predictions from the re-calibrated models, with predictions from separately fitted cohort-specific joint models (Appendix S2.1: Fig. S7). The difference in predictions was lowest in the Hopkins cohort (impact of PSA on upgrading risk similar to PRIAS). Comprehensive results are in Appendix S1.3 and Appendix S2.

Personalised Biopsy Schedules

We used the PRIAS-based fitted model to create personalised biopsy schedules for real PRIAS patients. Particularly, first using the model and patient's observed data; we predicted his cumulative upgrading risk (Fig. 5) on all of his future follow-up visits (biannually in PRIAS). Subsequently, we planned biopsies on those future visits where his conditional cumulative upgrading risk was more than a certain threshold (see Appendix S3 for mathematical details). The choice of this threshold dictates the timing of biopsies in a risk-based personalised schedule. For example, personalised schedules based on 5% and 10% risk thresholds are shown in Fig. 5, and in Appendix S3.1: Figs S10–S12.

To facilitate the choice of a risk threshold, and for comparing the consequences of opting for a risk-based schedule vs any other schedule (e.g. annual, PRIAS), we predict expected time delay in detecting upgrading for following a schedule. We were able to predict this delay for any schedule. For example, in Panel C of Fig. 5, the annual schedule has the least expected delay. In contrast, a personalised schedule based on a 10% risk threshold has a slightly larger expected delay, but it also schedules much fewer biopsies. An important aspect of this delay is that it is personalised as well. That is, even if two different patients are prescribed the same biopsy schedule, their expected delays will be different. This is because delay is estimated using all available clinical data of the patient (Appendix S3). While the timing and the total number of

Fig. 4 Model validation results. Panel **A**: time-dependent AUC (measure of discrimination). AUC at 1 year is not shown because we do not intend to replace the confirmatory biopsy at 1 year. Panel **B**: calibration-at-large indicates model miscalibration. This is because solid lines depicting the non-parametric estimate of the cause-specific cumulative upgrading risk [30], and dashed lines showing the average cause-specific cumulative upgrading risk obtained using the joint model fitted to the PRIAS dataset, are not overlapping. Re-calibrating the baseline hazard of upgrading resolved this issue (Appendix S2.1: Fig. S6). 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; UCSF, University of California San Francisco AS.



planned biopsies denote the burden of a schedule, a shorter expected time delay in detecting upgrading can be a benefit. These two, along with other measures such as a patient's comorbidities, anxiety, etc., can help to make an informed biopsy decision.

Web-application

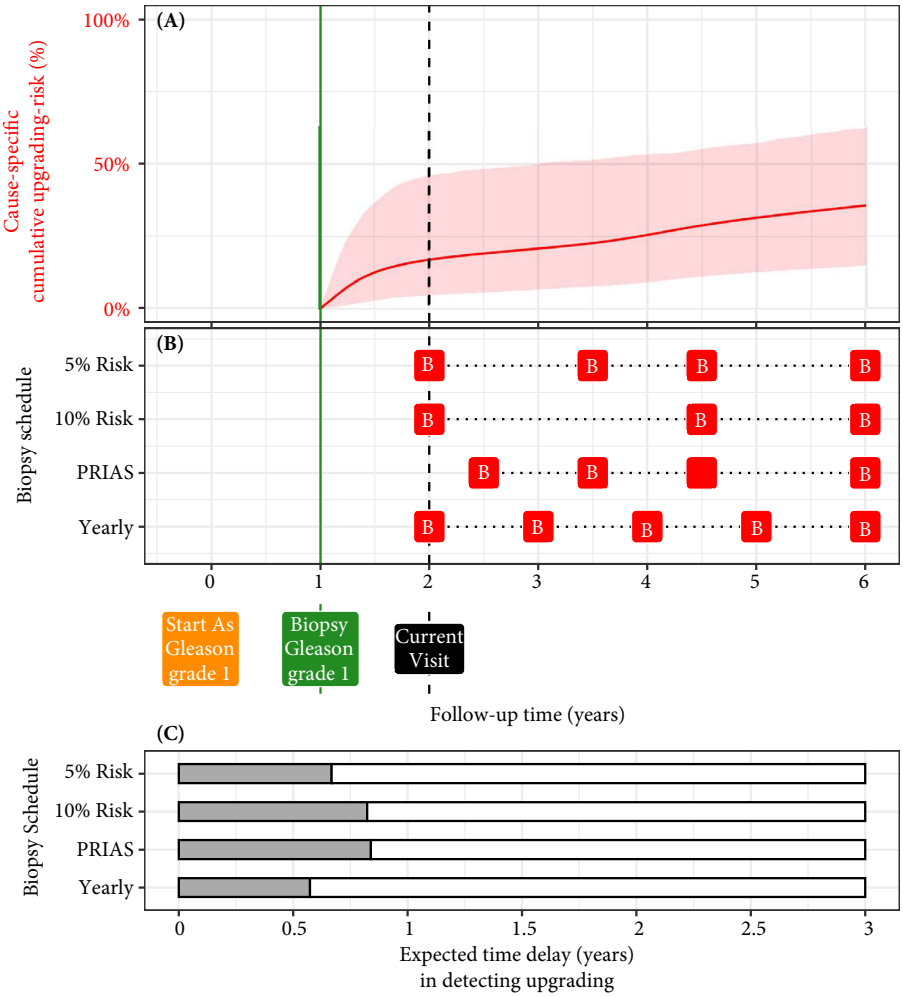
We implemented the PRIAS-based model, re-calibrated models for GAP3 cohorts, and personalised schedules in a user-friendly web-application https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/. This application works on both desktop and mobile devices. Users must first choose the cohort to which the patient belongs (left panel), and then upload patient data in Microsoft Excel format. Internally, the web-application loads the appropriate validated and re-calibrated model for that cohort. The maximum follow-up time up to which predictions can be obtained depends on each cohort (Appendix S2.1: Table S9). The web-application supports personalised, annual, and PRIAS schedules. For personalised schedules, users can control the choice of risk threshold. The web-application also compares the resulting risk-based schedule's timing of biopsies, and expected time delay in detecting upgrading, with annual and PRIAS schedules, to enable sharing biopsy decision-making.

Discussion

We successfully developed and externally validated a statistical model for predicting upgrading risk [3] in prostate cancer AS, and providing risk-based personalised biopsy decisions. Our present work has four novel features over earlier risk calculators [14,15]. First, our model was fitted to the world's largest AS dataset, PRIAS, and externally validated in the largest six cohorts of the Movember Foundation's GAP3 database [18]. Second, the model predicts a patient's current and future upgrading risk in a personalised manner. Third, using the predicted risks, we created personalised biopsy schedules. We also calculated the expected time delay in detecting upgrading (less is beneficial) for following any schedule. Thus, patients/doctors can compare schedules before making a choice. Fourth, we implemented our methodology in a user-friendly web-application (https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/) for both PRIAS and the validated cohorts.

Our present model and methods can be useful for numerous patients from PRIAS and the validated GAP3 cohorts (nearly 73% of all GAP3 patients). The model utilises all repeated PSA measurements, results of previous biopsies, and baseline characteristics of a patient. We could not include MRI and

Fig. 5 Illustration of personalised and fixed schedules of biopsies for the patient from Figure 3. Panel **A**: Predicted cumulative upgrading risk (95% credible interval shaded). Panel **B**: Different biopsy schedules with a red 'B' indicating a future biopsy. Risk: 5% and Risk: 10% are personalised schedules in which a biopsy is planned whenever the conditional cause-specific cumulative upgrading risk is above 5% or 10% risk, respectively. Smaller risk thresholds lead to more frequently planned biopsies. Green vertical line at 1 year is the time of the latest negative biopsy. Black dashed line at 2 years denotes the time of the current visit. Panel **C**: Expected time delay in detecting upgrading (years) if patient progresses before 6 years. The maximum time delay with limited adverse consequences is 3 years [13]. A compulsory biopsy was scheduled at 6 years (maximum biopsy scheduling time in PRIAS, Appendix S3) in all schedules for a meaningful comparison between delays.



PSA density because of sparsely available data in both the PRIAS and GAP3 databases. But, our present model is extendable to include them in the near future. A benefit of our present model is that it allows the biopsy schedule, schedule of longitudinal measurements, and loss to follow-up in each cohort to depend on patient age and PSA characteristics. Consequently, in future, when MRI data is included in the model, our model will also accommodate biopsy schedules dependent on MRI data or MRI schedules dependent on previous biopsy results, PSA characteristics, and age of the patient (mathematical proof in Appendix S1.2). An additional advantage of our present model and resulting personalised schedules is that they update as more patient data becomes available over follow-up. The current discrimination ability of our model, exhibited by the time-dependent AUC, was between 0.6 and 0.7 over-follow. While this is moderate, it is also so because unlike the standard AUC [28] the time-dependent AUC is more conservative, as it utilises only the validation data available until the time at which it is calculated. The same holds for the time-dependent MAPE, although MAPE varied much more between cohorts than the AUC. In cohorts where the effect size for the impact of PSA level and velocity on upgrading risk was similar to that for PRIAS (e.g. Hopkins cohort), the MAPE was moderate. Otherwise, the MAPE was large (e.g. KCL and MUSIC cohorts). We required re-calibration of our model's baseline hazard of upgrading for all the validation cohorts.

The clinical implications of our present work are as follows. First, the cause-specific cumulative upgrading risk at the 5-year follow-up was at most 50% in all cohorts (Panel B, Fig. 4). That is, many patients may not require some of the biopsies planned in the first 5 years of AS. Given the non-compliance and burden of frequent biopsies [7], the availability of our methodology as a web-application may encourage patients/doctors to consider upgrading risk-based personalised schedules instead. Despite the moderate predictive performance, we expect the overall impact of our model to be positive. There are two reasons for this. First, the risk of adverse outcomes because of personalised schedules is quite low because of the low rate of metastases and prostate cancer specific mortality in AS patients (Table 1). Second, studies [8,31] have suggested that after the confirmatory biopsy at 1 year of follow-up, biopsies may be done as infrequently as every 2–3 years, with limited adverse consequences. In other words, longer delays in detecting upgrading may be acceptable after the first negative biopsy. To evaluate the potential harm of personalised schedules, we compared them with fixed schedules in a realistic and extensive simulation study [32]. We concluded that personalised schedules plan, on average, six fewer biopsies compared to annual schedule and two fewer biopsies than the PRIAS schedule in slow/non-progressing AS patients, while maintaining almost the same time delay in detecting upgrading as the PRIAS schedule. Personalised schedules with different risk thresholds indeed have different performances across cohorts. Thus, to assist patients/doctors in choosing between fixed schedules and personalised schedules based on different risk thresholds, the web-application provides a patient-specific estimate of the expected time delay in detecting upgrading, for both personalised and fixed schedules. We hope that access to these estimates will objectively address patient apprehensions regarding adverse outcomes in AS. Last, we note that our web-application should only be used to decide biopsies after the compulsory confirmatory biopsy at 1 year of follow-up.

This work has certain limitations. Predictions for upgrading risk and personalised schedules are available only for a currently limited, cohort-specific, follow-up period (Appendix S2.1: Table S9). This problem can be mitigated by re-fitting the model with new follow-up data in the future. Recently, some cohorts started utilising MRI to explore the possibility of targeting visible lesions by biopsy. Presently, the GAP3 database has limited PSA density and MRI follow-up data available. As PSA density is used as an entry criterion in some AS studies, including it as a predictor can improve the model. In this regard, the present model can be extended to include both MRI and PSA density data as predictors when they become available in the future. Our model schedules biopsies in a personalised manner, but the patient burden can be decreased even more if we also personalise the schedule of PSA measurements. A caveat of doing so is that reduction in the number of PSA measurements can also lead to an increase in the variance of risk estimates, and also affect the performance of personalised schedules. Although we have done a simulation study to conclude that personalised schedules may not be any more harmful than PRIAS or an annual schedule [32], with an infrequent PSA schedule, these conclusions may not hold. Hence, we do not recommend any changes in the schedule of PSA measurements from the current protocol of PSA measurements every 6 months. At the same time, personalising the schedule of both biopsies and PSA measurements together is a research problem we intend to tackle in the near future. We scheduled biopsies using cause-specific cumulative upgrading risk, which ignores competing events such as treatment based on the number of positive biopsy cores. Employing a competing-risk model may lead to improved personalised schedules. Upgrading is susceptible to inter-observer variation too. Models that account for this variation [14,33] will be interesting to investigate further. Even with an enhanced risk-prediction model, the methodology for personalised scheduling and calculation of expected time delay (Appendix S3) need not change. Last, our web application only allows uploading patient data in Microsoft Excel format. Connecting it with patient databases can increase usability.

Conclusions

We successfully developed a statistical model and methodology for predicting upgrading risk, and providing risk-based personalised biopsy decisions, in prostate cancer AS. We externally validated our model, covering nearly 73% patients from the Movember Foundations' GAP3 database. The model, made available via a user-friendly web-application (https://emcbiostatistics.shinyapps.io/prias_biopsy_recommender/), enables shared decision-making of biopsy schedules by comparing fixed and personalised schedules on total biopsies and expected time delay in detecting upgrading. Novel biomarkers and MRI data can be added as predictors in the model to improve predictions in the future. Re-calibration of baseline upgrading risk is advised for cohorts not validated in this work.

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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, Steyerberg, and Rizopoulos. Administrative, technical or material support: Nieboer. Supervision: Roobol, and Rizopoulos. Other: none.

Conflicts of Interest

The authors do not report any conflict of interest, and have nothing to disclose.

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Appendix A

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Abbreviations: AS, active surveillance; AUC, area under the receiver operating characteristic curve; GAP3, Movember Foundation's third Global Action Plan; GGG, Gleason Grade Group; (a)HR, (adjusted) hazard ratio; KCL, King's College London; MAPE, mean absolute risk prediction error; MSKCC, Memorial Sloan Kettering Cancer Center; MUSIC, Michigan Urological Surgery Improvement Collaborative; PRIAS, Prostate Cancer Research International Active Surveillance; UCSF, University of California San Francisco.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. A joint model for the longitudinal PSA, and time to Gleason upgrading.
Appendix S1.1. Assumption of *t*-distributed (d.f. = 3) error terms.
Appendix S1.2. PSA-dependent biopsy schedule of PRIAS, and competing risks.
Appendix S1.3. Results.
Appendix S2. Risk predictions for upgrading.
Appendix S2.1. Validation of risk predictions.
Appendix S3. Personalised biopsies based on cause-specific cumulative upgrading risk.
Appendix S3.1. Expected time delay in detecting upgrading.
Appendix S4. Web-application for practical use of personalised schedule of biopsies.
Appendix S5. Source code.
Appendix S5.1. Fitting the joint model to the PRIAS dataset.
Appendix S5.2. Validation of predictions of upgrading.
Appendix S5.3. Creating personalised schedules of biopsies.
Appendix S5.4. Source code for web application.