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Your Submission EURUROL-D-20-00194

2 messages

European Urology <em@editorialmanager.com> 26 February 2020 at 02:55
Reply-To: European Urology <platinum@europeanurology.com>
To: Anirudh Tomer <anirudhtomer@gmail.com>

Our web site: https://www.editorialmanager.com/eururol/

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RE: EURUROL-D-20-00194 A Ready To Use Web-Application Providing a Personalized Biopsy Schedule for Men With Low-Risk PCa Under Active Surveillance

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Dear Mr Tomer,

Thank you for submitting the manuscript listed above to European Urology.

Your article has been evaluated by our expert reviewers and you can see their comments below. We are afraid that after having carefully considered all of the comments, we will not consider your article for publication. Our journal is under pressure to publish the most important information as rapidly as possible. Papers therefore have to be judged not only on their scientific quality but also on many other standards related the target readership of The Platinum Journal.

This is definitely not a reflection on the quality of the work undertaken, but is due to the increasing competition for space in European Urology - we accept less than 10% of all submissions.

However, we do think your manuscript could be considered by our newly launched journal European Urology Open Science (EU Open Science)
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Should you accept this transfer, you will have the opportunity to revise your paper, taking into account the reviews received from "European Urology". The revision will take place after your paper has been transferred to the new journal but before it is assigned to an Editor.

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WE ALSO ASK THAT THE REVISED MANUSCRIPT SHOW THE TRACKING MARKS OF CHANGES MADE FROM THE ORIGINALLY REVIEWED VERSION.

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While we are aware that you may not necessarily agree with our decision, we count on your understanding. We thank you very much for your interest in our journal and we hope you will again consider us when submitting your manuscripts in the future.

Yours sincerely,

James Catto Giacomo Novara
Editor-in-Chief Associate Editor

Reviewer #1: Thank you for your submission entitled, "A Ready To Use Web-Application Providing a Personalized Biopsy Schedule for Men With Low-Risk PCa Under Active Surveillance." In this manuscript, the authors present a risk prediction model and accompanying web application to generate a personalized biopsy schedule in the active surveillance of low risk PCa:

1. The PRIAS dataset is well known along with the validation cohorts from the Movember GAP3 database. These are large datasets reflective of many institutions and jurisdictions.

2. The impact of these results may change substantially with the introduction of MRI. The authors acknowledge this appropriately in the manuscript but remains a limitation in the utility of this prediction model.

3. Application interface: The web application is very interesting. However, from a functional perspective, the application is somewhat difficult to use. It is relatively difficult to enter patient data (dates) and may take a long time in clinic. For example, the PSA dates and values themselves are not merged and could easily be misaligned.

4. The generalizability of the model may be limited in real-world settings. As the authors note, amongst the cohorts, there was very different risks of upgrading at 5 years and the model needed to be recalibrated to the baseline risk in each cohort as each was different. For patients outside these cohorts, baseline risk cannot be recalibrated for them and limits its broader applicability.

5. The final model has moderate AUC values and prediction error/MAPE. In particular, the MAPE in early years can be quite substantial, up to 0.46, in the individual cohorts. This may be a result of a misclassification of underlying risk and underscores the likely necessity of confirmatory biopsy. Following this period, the MAPE drops significantly. Would this model be better applied in a more uniformly low risk, well sampled group after confirmatory biopsy (for a personalized strategy on biopsy # >2)? This may also make the cohorts more homogenous.

6. The number of preventable biopsies may be overstated versus the real world. As biopsies eclipse 3-4 biopsies, patients are often less willing to undergo these outside of a trial setting. As such, the number of avoided biopsies is likely lower (in addition to the increased uptake of MRI).

7. Patient preferences are taken into account only at 5/10/15% thresholds of risk tolerance. In real world practice, patient preferences extend beyond risk tolerance alone, and include the risk of complications, anxiety, trust in non-invasive forms of detection, previous experience with biopsy, etc. These have been described in the literature. Although this is beyond the scope of this study, this should be mentioned in the discussion and limitations.

8. The methods describe that the timing of biopsies is included in the modelling. Did the authors explore also including the number of previous biopsies as a predictor?

Reviewer #2: This is a retrospective cohort study assessing the variables associated with Gleason Grade Group (GG) upgrading in patients with favoravle risk (very low and low risk) prostate cancer (PCa) managed with active surveillance. The authors used the Prostate Cancer International Active Surveillance (PRIAS) cohort to develop regression model to identify variables associated with risk of progression. The model was then externally validated in six cohorts of Movember Foundation's GAP3 database. The regression model was used to develop a web-based application to help patients and physicians by providing risk-based personalized biopsy decisions, in prostate cancer AS.

Only patients with GG1 in PRIAS database (n=7813) at initial biopsy were selected. The primary event of interest was cancer upgrading (GG≥2) at subsequent biopsies. Other reasons for under going definitive treatment, based on PSA kinetics, cancer volume and anxiety were not considered. A joint model for time-to-event and longitudinal data was proposed to capture within-patient correlation for PSA, the association between the Gleason grades and PSA profiles of a patient, and handling missing PSA measurements after a patient experienced upgrading. The cause-specific cumulative upgrading-risk at year of follow-up was 35% in PRIAS and at most 50% in validation cohorts. The strongest predictor of upgrading-risk was instantaneous PSA velocity (aHR 2.47 95%CI: 1.93-2.99). For each decade increase in age the risk of upgrading was 1.45 (aHR 1.45 95%CI: 1.30-1.63) and for 0.5 increase in PSA the aHR was
0.99 (95%CI: 0.89-1.11). In validation cohorts, time-dependent AUC was moderate (0.55 to 0.75) over the whole follow-up period. Time-dependent MAPE was large (0.3 to 0.45) in those co-
cohorts where the impact of PSA on upgrading-risk was different from PRIAS and moderate (0.1 to 0.3) otherwise. In all cohorts, the MAPE decreased rapidly after year one of follow-up. A personalized biopsy schedule was then proposed using different biopsy thresholds. The expected time delay in detecting upgrading if the patient progresses before the time of the last planned biopsy was calculated based on different biopsy schedules. Interestingly, when biopsy threshold was put at 5% risk of upgrading, 1 biopsy was omitted compared to annual biopsy with no significant delay in diagnosis. Similarly, if biopsy threshold was put at 10%, compared to PRIAS biopsy schedule the patient would undergo 1 less biopsy while the time to diagnosis of upgrading is almost the same.

This study is of interest as it proposes a tool to personalize the biopsy schedule for patients on AS, however, the overall concept and findings are not novel (predicting risk of upgrading for AS candidates). The authors used a complex statistical model to identify variables associated with risk of upgrading on subsequent biopsy. The strengths of the study are large training and validation patient population, appropriate statistical method which uses a cumulative data over the follow-up period to enrich itself, and the model validation in different AS cohorts (with different enrolment and surveillance protocols).
However, the study is limited by few important factors:1- the authors did not include baseline and follow up data/characteristics known to be associated with risk of upgrading (cancer volume, PSA density) in the proposed model, 2- MRI is increasingly implemented in daily urology practice including AS. Lack of information on MRI findings significantly limits clinical utility of proposed model and application, 3- although the use of genomic markers is not agreed upon by experts but recent statement by the ASCO encourages the use of genomic markers in patients who deemed at higher risk of harboring higher grade disease at baseline (higher volume). This is another limitation of the study which should be highlighted. 4-

Comments:
Title/Abstract:
1- Spell out abbreviations when used for the 1st time (PRIAS).

Introduction:
1- Spell out abbreviations when used for the 1st time (PRIAS).

Methods:
1- Although I agree with the argument that grade progression is a predictor of oncologic outcomes, it is known from published AS cohort studies that volume progression is associated with higher risk of grade progression at follow up biopsy. Additionally, based on ERSPC findings patients with low risk PCa are at a higher risk of biochemical recurrence after treatment compared to very-low risk PCa patients. So not including volume characteristics of the disease at baseline and subsequent biopsies is likely to limit the predictive ability of the proposed model.

Results:
None

Discussion:
The study is limited by few important factors (some are highlighted by the authors):
1- the authors did not include baseline and follow up data/characteristics known to be associated with risk of upgrading (cancer volume, PSA density)
2- MRI is increasingly implemented in daily urology practice including AS. Lack of information on MRI findings significantly limits the clinical utility of proposed model and application

3- although the use of genomic markers is not agreed upon by experts but recent statement by the ASCO encourages the use of genomic markers in patients who deemed at higher risk of harboring higher grade disease at baseline (higher volume). This is another limitation of the study which should be highlighted.

Reviewer #3: The authors have used PRIAS data to develop an "app" that predicts the likelihood of disease upgrading and therefore the need for prostate biopsy.
Concerns raised by their paper are several.
1) The model relies heavily on PSA changes over time. How do the authors adjust for patients that have psa values that vary widely as compared to those patients with psa's that are virtually constant? Anyone who has followed patients on active surveillance quickly realizes that psa's can vary considerably. Some go up and return to baseline a month or two later.
2) MRI has become a standard tool in most active surveillance protocols. This missing data seriously compromises the model.
3) The follow up time for the model is surprisingly short - barely 4 years. How can the authors be confident that trends will continue at the same rate over time. As stated in the manuscript, many clinicians routinely offer a biopsy at year one, but base subsequent biopsies on psa trends and MRI reports. Therefore building a model around just 2 consecutive biopsies raises concerns.

Reviewer #4: The authors sought to create a personalized biopsy schedule based on age and PSA velocity for patients on active surveillance. They used the PRIAS study to build and then several cohorts with GAP3 to validate. They observed the estimated risk of upgrading by 5 years ranged from 35-50%. However, the model AUC validated modestly ranging from 0.55- 0.75.

The concept is intriguing and the web-based calculator has potential however I have some concerns.

1) I have some concerns about how certain variables/factors in active surveillance that we know are associated with progression have been handlded.
a. Confirmatory biopsy: it is customary now to obtain a repeat biopsy within the first year. Up to 30% of patients may upgrade at that biopsy. The remaining hten go on surveillance. I see no mention of confirmatory biopsies and how they were handled in this paper.
b. Often biopsies on AS will come back negative and we know this is associated with lack of progression later on in AS. I see no capacity for the model to handle a negative biopsy.
c. Basing the model on the PRIAS schedule of 1yr, 4yrs, 7yrs and 10yrs….concerns that there are delays in detecting progression and that the cumulative risk model will underestimate risk
d. I understand the argument for why you only looked at upgrading based on biopsy. However, if we ignore people that went for RP and found ISUP 2 or higher disease, shouldn't this be factored into the models. By excluding them won't we lead to an underestimate of risk?
e. The lack of MRI data is acknowledged in the limtations. However, I think this is unfortunately a major limitation. Most active surveillance now is practiced with MRI - this drastically changes baseline risk of upgradeing and moreover the information from follow-up MRIs (e.g. a new leseion) is correlated with upgrading.
f. The number of cores positive and percent of cores seems to be completely ignored in models yet is an important predictor of upgrading. I would suggest incorporating this information, especially on subsuequent biopsies to update realtime risk estimates.
g. 334 men transitioned to watchful waiting - how was this handled in the models? Presumably these men never had follow-up biopsies.
h. The median biopsies per patient is shockingly low at 2…many of the validation cohorts it's only 1. I'm not sure how we can build an accurate model predicting upgrading with the majority only having 1-2 biopsies on surveillance.
2) Abstract is choppy language and makes for harder reading. Also hard to follow and understand, e.g. the sentence starting "Moderate prediction error (0.1-0.3)….". This sentence is confusing and should be clarified. The whole abstract is quite cumbersome to read through.
3) If possible, please be more precise than ">100 centers" in table 1
4) The first statement of the results is awkward - you state the cumulative 5-year risk of upgrading is 35-50%....and then go on to editorialize by saying, many men don't need the biopsies before 5 years. I would save the latter for discussion section. And also, even at 35% risk at 5 years, I would argue they still need biopsies.
5) I found the web-interface difficult to use - the need to input dates and values separated by commas etc.

Reviewer #5: The subject is timely and clinically relevant.
The Abstract, with multiple abbreviations, is poorly written and at times, almost incomprehensible.
The manuscript is unfocused. The authors should probably concentrate on the development and validation of the prediction model. The web-based application can be a separate communication.
The anecdotal illustrations (Figures 1 and 2) of a typical clinical course and possible delay in detection of upgrading and the rationale for personalized biopsy schedules probably work well for some other non-urological journals, but not very informative for the EU readership.
The concept of instantaneous PSA velocity as an prognostic indicator is noteworthy. The detailed description of the

model and the personalized schedules etc. would be best presented in a different forum.
Would the predictive model having a rather modest discrimination ability (AUC as low as 0.55), is it a bit premature to implement that on a wide scale? It is understandable to apply on a trial basis with a well-defined and closely followed cohort, i.e. the PRIAS patients. (Even so, it was stated the model was useful for "numerous patients from PRIAS and validated cohorts" ….how many? How were they selected? ALL PRIAS patients?) To advertise as a widely available web application may seem premature.
The authors should be aware that most practitioners in fact follow a more "personalized schedule as opposed to a rigid "frequent i.e. annual" biopsy schedule.

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Ani Rudh <anirudhtomer@gmail.com> 26 February 2020 at 08:07
To: "D. Rizopoulos" <d.rizopoulos@erasmusmc.nl>

Good morning Dimitris,
FYI. Our article was not accepted. Will send to others after discussing with you.
[Quoted text hidden]