Editorial

Men on active surveillance without cancer on biopsy are less likely to reclassify

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The manuscript of Kearns *et al.* based on data from the multicenter Canary Prostate Active Surveillance Study (PASS) reports on surveillance biopsies with benign result as prognostic marker for less reclassification to higher risk disease (1). The PASS cohort included men from 2008 with clinically localized low risk prostate cancer (cT1-2c disease, no previous treatment, and Gleason ≤3+4 disease). Prostate-specific antigen (PSA) was measured every 3 months, and a minimum of 10 core ultrasound-guided biopsies was performed at 6–12 months after diagnosis, 24 months, and then every 2 years. Reclassification was defined as an increase in primary or secondary Gleason grade, or an increase in tumor volume to ≥34% of the total biopsy cores involved. The authors used Cox proportional hazards modeling to associate previous biopsy findings with future reclassification outcome. In addition to first and second biopsy findings other covariates were considered: PSA measurement closest to biopsy, diagnostic PSA, maximum tumor core ratio, prostate volume, clinical T-stage, diagnostic Gleason score, body mass index (BMI), age at diagnosis, and race. In total 657 men were included of whom 214 (33%) had no cancer on their first active surveillance biopsy, 282 (43%) had cancer but did not reclassify, and 161 (25%) were reclassified. With a median follow-up of almost 3 years, the authors found that men who had a consistent negative biopsy (no cancer present) compared to men with a biopsy confirming the Gleason grading at time of diagnosis had a lower risk of future reclassification (hazard rate 0.50, P=0.008) after adjustment for PSA (prior to biopsy), prostate volume, and BMI. The authors suggest to include the surveillance biopsy results into a tailored risk-based active surveillance schedule which might reduce the number of biopsies during active surveillance by lengthening the biopsy interval.

The main goal of active surveillance is to safely reduce overtreatment and is the preferable option for the initial management of men with localized low-risk prostate cancer (2,3). The active surveillance cohort by Klotz *et al.* has one of the longest follow-up periods available. It was concluded that active surveillance is safe and has similar mortality rates in low-risk patients managed with initial definitive intervention (4). The downside of active surveillance is that biopsies come with the risk of infection, are burdensome for the patients, and are costly (5). Most likely for these reasons prostate biopsy compliance decreases with increased duration of the active surveillance protocol (6). This asks for a change towards a more tailored approach where the frequency of biopsy taking should be reduced safely, without losing the time-to-cure window.

Sufficient long-term data on outcomes after secondary treatment [e.g., prostatectomy or radiation therapy] is preferred to provide concrete recommendations, while active surveillance cohorts still need to mature, reclassification on prostate biopsy specimen is being used as a proxy. To predict the presence of clinically significant prostate cancer on biopsy risk-based methods have been published to optimize active surveillance (7). Prediction in a homogeneous group, as men on active surveillance patients are, is not easy as is shown by the poor performance of previously developed predictive models with area under

the receiver operating characteristic (ROC) curves ranging from 0.52 to 0.75 (8,9).

To improve this prediction Kearns *et al.* included prostate biopsy results at year 1 and 2 of the active surveillance period. They found a 50% reduction of risk of future reclassification when no cancer was found on first biopsy (3–24 months since diagnosis), and an 82% decreased risk without cancer on the second active surveillance biopsy (6–24 months since previous biopsy). This concept of previous biopsy without cancer makes sense: cancer is a growth process and so it is expected that men on active surveillance who have a biopsy showing no cancer truly have a low volume prostate cancer and thus a reduced risk of developing worse disease in the future. However, the authors acknowledge that their report might be limited by the number of men who did not reclassify (n=494 and n=259 on first and second biopsy, respectively) and that the follow-up of the remaining men at risk of a reclassification event is relative short. Still this finding of the potential predictor is in concordance with a previously published study by Kovac *et al.* (10) and highlights the prognostic value of confirmatory biopsy (first biopsy during active surveillance). As they found a reduced reclassification rate at subsequent surveillance prostate biopsies in those men who underwent confirmatory biopsy that was negative compared to men who did not underwent a confirmatory biopsy.

To generalize the prognostic value of previous biopsies findings, it should be viewed within the context of the current literature of other active surveillance cohorts. As different inclusion criteria, follow-up schedules, and definitions of progression are available for active surveillance (11,12). The PASS cohort uses both grade and/or tumor volume. Wong *et al.* found that no cancer on the confirmatory biopsy decreased the risk of volume-related, but not grade-related progression (13). Here, the grade-related progression is reported independently of total reclassification, i.e., excluding men reclassified based on tumor volume to ≥34% of total biopsy cores. In this sensitivity analysis surveillance biopsy without cancer was no longer significant (P=0.07) in predicting future reclassification. It is not surprising that men with low volume prostate cancer, who might present the majority of men without cancer on confirmatory biopsy, are less likely to progress on the tumor volume criteria and also on grade criteria as low volume cancer are more difficult to biopsy. More importantly, grade-related progression still occurred in the no-cancer group (±20%) after first biopsy and 5% showed progression after the second negative biopsy. Since biopsy cannot be completely abandoned, this leaves us with the question how long we safely can wait? Unfortunately, the authors cannot answer this question with their analysis, because all patients followed the same biopsy schedule, longer follow-up is needed, and hard end outcomes such as metastasis and prostate cancer death were not included.

Furthermore, due to the considerable variation in currently applied active surveillance protocols the association between negative surveillance biopsy and decreased risk of reclassification might be different and not applicable in other settings. The Prostate Cancer Research International Active Surveillance (PRIAS) protocol proposes to perform repeat biopsies with extended intervals, i.e., at 1, 4, 7, and 10 years after diagnosis, and found similar reclassification rates during follow-up (14). This questions whether the PASS follow-up protocol was too strict to begin with, as biopsy intervals could have already been extended with at least 1 year and maybe more. On the other hand, in the Johns Hopkins active surveillance cohort repeat biopsy was performed annually, a lower risk of grade reclassification was found for a higher number of previous biopsies without reclassification (odds ratio 0.68, P<0.01) (15). How would this finding change when biopsies would be performed every other year instead of annually? These variations in protocol should be considered next to additional factors such as clinical characteristics, biopsy history, imaging and genomic data. All these factors should be incorporated into a dynamic model to further improve patient selection for active surveillance and their follow-up schedule. Incorporation of the available multiparametric MRI (mpMRI) information is expected to alter patient selection and especially reduce under-grading (16-18). This could potentially result in the inclusion of true low-grade prostate cancer and as such affect the strict follow-up program for men on active surveillance. The role of mpMRI in delaying subsequent biopsies is still not certain, although it is increasingly being used in this manner (19). Undergrading of prostate cancer in men with low-risk disease at initial biopsy is widely recognised, and confirmatory biopsies are advocated within the first year of diagnosis.

To summarize, the finding that no cancer on an active surveillance biopsy would have a lower reclassification rate could be another predictor in refining an active surveillance algorithm, but may be hard to use in daily practice as this finding is dependent on the underlying follow-up schedule. External validation or similar findings within different active surveillance cohorts are required.

Adaptations to the active surveillance protocol are desirable to limit unnecessary biopsies. This can be achieved by properly selecting patients for active surveillance using risk stratification based on clinical features (i.e., life expectancy, PSA, diagnostic biopsy results) and should be prospectively conducted. While we keep on searching for novel predictors to improve the decision-making process in active surveillance, active surveillance safely minimizes unnecessary treatment for men with low-risk prostate cancer and achieves a high quality of life.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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