Editorial

Genomic scores are independent of disease volume in men with favorable risk prostate cancer—implications for choosing men for active surveillance

Guillaume Ploussard[1,2], Ambroise Salin[1], Igor Latorzeff[3]

[1]Department of Urology, Saint Jean Languedoc Hospital, Toulouse, France; [2]Division of Uro-Oncology, Institut Universitaire du Cancer Toulouse, Toulouse, France; [3]Department of Radiation Oncology, Clinique Pasteur, Toulouse, France

Correspondence to: Guillaume Ploussard. Department of Urology, Saint Jean Languedoc Hospital, 20 route de Revel, Toulouse 31400, France. Email: g.ploussard@gmail.com.

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For low-risk prostate cancer, active surveillance (AS) has been increasingly proposed as the preferential initial management strategy. AS entails a strategy by which selected men are managed expectantly with the intention to apply potentially curative treatment in case of progression signs (1). Progression mainly occurs during the 2 first years with differed treatment rates ranging from 20% to 40% among prospective series (1,2). This "rapid" progression could be explained by a not ideal initial selection rather than a real pathological progression of truly very low risk prostate cancer. Thus, for treatment decisions and inclusion of patients in AS protocols, clinicians have to deal with this clinically meaningful risk of reclassification (3-5).

Unfortunately, a consensus about the most relevant definition of low risk cancer remains elusive for men who are amenable to AS. Biopsy criteria such as the number of positive cores, tumor length (total or at any core), or percentage of cancer involvement at any core are predictive factors of tumor volume in radical prostatectomy specimens or biochemical failure after radical treatment, and, to date, are yet the main criteria used in AS protocols. Thus, published AS series used different inclusion criteria largely based on centre experiences and preferences with no hard data (1,2). However, the definition of low tumour volume/involvement strongly varies among AS program, with a relatively comparable reclassification risk whatever the retained pathologic criterion used.

How to explain this difficulty to accurately identify the truly insignificant prostate cancer? The two main explanations are probably the difficulty to precisely identify the disease molecular behavior by standard pathological tools on the one hand, and the imperfection for targeting the most aggressive part of the tumour by our standard random biopsy scheme on the other hand. However, hopefully, the future AS studies should better identify the subgroup of low risk prostate cancer men, by assessing more accurate molecular prognostic markers and imaging-based diagnostic strategies. Nevertheless, daily practice-changing studies are still awaited.

One example is the urine prostate cancer gene 3 prognostic marker that has been correlated to disease volume in low risk cancers and has been suggested to better characterize the potential aggressive behaviour of supposed low-risk prostate cancers (6,7). Unfortunately, these promising results were not significantly correlated with the reclassification risk in AS cohorts (8). Indeed, the use of a single molecular marker is probably doomed to failure. That's why genomic tests using a panel of several genes are considered as hopeful candidates.

In the present series, from a large series of AS patients whom positive cores were tested for genomic scores, the authors have assessed the correlation between tumour

volume on biopsies and genomic scores (9). We congratulate the authors for their findings that tended to demonstrate that genomic scores (17-gene panel, OncotypeDx™) could be of great interest at initial AS selection. Such a molecular-based prognostic assessment was not correlated with biopsy tumour volume (that was the main objective of this study) and thus, could offer an independent predictive value in addition to usual selection criteria. The genomic prostate score reclassified low risk to intermediate risk cancer in 7.2% of cases, and very low risk to low risk cancer in 6.3% of cases. These reclassification rates were in line with previous published findings confirming the reproducibility and the homogeneity of this test. Another important finding was that the genomic score confirmed the weak aggressiveness of prostate cancer in a large proportion of cases, with 43% of low risk cancers that were reclassified as very low risk tumours by the genomic prostate score. This score could be used as a reassurance tool for patients and physicians, aiming at lightening subsequent monitoring and improving AS compliance rates.

This study demonstrates that the genomic prostate score helps in reclassifying at inclusion a not negligible proportion of patients and that the prognostic information it gives are independent to those provided by tumour volume and involvement on biopsies. Nevertheless, before a wide acceptance of genomic scores in AS protocols, several limitations have to be highlighted. The main endpoint used in this study was the likelihood of favourable pathology that is a probability calculated from the initial iterations of the OncotypeDx™ test results. And this is surely not the best end point to address conclusion in men eligible for AS. This probability has been evaluated in cohorts of patients receiving radical treatments, and to the best of our knowledge, has never been correlated with outcomes in men managed by AS. The genomic tests correlate with pathologic features in radical prostatectomy specimens, biochemical failure, metastatic disease, and mortality after radical treatment. However, only extrapolations can be considered when using this test in an AS cohort. The authors assessed the reclassification rate based on this genomic testing, whereas the optimal reclassification rate should have been reported using biopsy control findings. We cannot state that genomic testing in low risk prostate cancers patients is a relevant surrogate for confirmatory biopsies or for differed treatment rates in AS programmes. The short follow-up of the present series is one explanation as well as the low number of patients undergoing differed radical prostatectomy. Indeed, the analysis of the radical prostatectomy specimens would have be interesting to confirm the correlations between disease volume on biopsies, genomic score, and pathologically confirmed tumour volume and aggressiveness in prostate specimens.

Thus, given that the main endpoint by definition depends on the genomic score testing, we cannot conclude on the inferiority of detailed biopsy characteristics, compared with genomic score, for the AS eligibility. Both information (biologic potential of the tumour measuring by genomic test, and extent of the disease assessed by biopsy features) are surely complementary for predicting reclassification rates and oncologic outcomes during conservative management.

Another pitfall of this genomic profile strategy is that gene analysis is only performed in a random part of the cancer (10). Indeed, the biopsy core number and location were not controlled and varied according to the physician. Moreover, as no data on pre-biopsy magnetic resonance imaging (MRI) and targeting was reported, we can imagine that only systematic random biopsies were performed. In that setting, we can easily believe that the genomic profile of the tumour may provide a not negligible prognostic value in addition to the Gleason score, by catching aggressive and "not visible" component of the disease, and then, by reclassifying cancers for which the random biopsies missed the most aggressive focus. The value of this genomic score remains doubtful when targeted cores can diagnose the true pathological grading of the disease.

The genomic testing is surely one of the main hopes in a near future for improving risk and prognosis assessment in prostate cancer field. Nevertheless, only long-term prospective studies comparing different inclusion criteria (imaging-based, molecular-based, volume-based) could answer the question of the ideal candidate for conservative management and definitely close the debate. This is also worthy to note, that, although the development of strict criteria based on predefined cut-offs of different variables would facilitate their use in the clinical practice, their lack of flexibility might eventually limit the number of patients potentially eligible for AS, thus exposing them to a non-negligible risk of overtreatment.

Until now, no specific molecular test, genomic score, or MRI-targeted biopsy software has definitively hit the mark. And whatever the prognostic tool used, we know that there is no such thing as zero risk. The reclassification risk will remain present justifying the monitoring strategy. By then, from our point, disease volume on biopsies should not be abandoned and still provides relevant prognostic features for decision on AS candidacy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272-7.
2. Bokhorst LP, Valdagni R, Rannikko A, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol 2016;70:954-60.
3. Gandaglia G, Ploussard G, Isbarn H, et al. What is the optimal definition of misclassification in patients with very low-risk prostate cancer eligible for active surveillance? Results from a multi-institutional series. Urol Oncol 2015;33:164.e1-9.
4. Ploussard G, Salomon L, Xylinas E, et al. Pathological findings and prostate specific antigen outcomes after radical prostatectomy in men eligible for active surveillance--does the risk of misclassification vary according to biopsy criteria? J Urol 2010;183:539-44.
5. Ploussard G, Xylinas E, Salomon L, et al. The role of biopsy core number in selecting prostate cancer patients for active surveillance. Eur Urol 2009;56:891-8.
6. Ploussard G, Durand X, Xylinas E, et al. Prostate cancer antigen 3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance. Eur Urol 2011;59:422-9.
7. Auprich M, Bjartell A, Chun FK , et al. Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. Eur Urol 2011;60:1045-54.
8. Tosoian JJ, Loeb S, Kettermann A, et al. Accuracy of PCA3 measurement in predicting short-term biopsy progression in an active surveillance program. J Urol 2010;183:534-8.
9. Nyame YA, Grimberg DC, Greene DJ, et al. Genomic Scores Are Independent of Disease Volume in Men with Favorable Risk Prostate Cancer: Implications for Choosing Men for Active Surveillance. J Urol 2018;199:438-44.
10. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol 2015;67:627-36.

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