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Time for a 'radical' change to Active Surveillance for prostate cancer…?

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Over the past two decades, Active Surveillance (AS) has become an acceptable management option for men with low-risk clinically localised prostate cancer. A thorough literature review published in this month's issue of European Urology shows that a plethora of factors influence whether men choose to undergo or stay on AS - ranging from individual patient characteristics such as age or cancer features, through family and social support, to attitudes communicated by clinicians and influences from healthcare organisations and policy directives.[1] These findings chime with other reviews showing the lack of consensus over fundamental aspects of AS programmes such as inclusion criteria, monitoring strategies and 'triggers' for change of management.[2] With such a diversity of approaches and influences, and recent transformational developments in the field, how should AS now be implemented?

The development of AS

The history of AS is relatively short and somewhat controversial. The concept was first discussed as a strategy distinct from 'watchful waiting' in the late-1990s - 'Active Surveillance' in North America[3] and 'Active Monitoring - AM' in the UK.[4] It started because of the realisation that many of the localised prostate cancers identified by increasingly widespread PSA testing were low-risk and posed little threat to a man's length of life,[5] yet most were being treated radically, with serious consequences for men's sexual, urinary and bowel function. Increasing numbers of men are now undergoing AS successfully, underpinned by evidence from a small number of well-characterised cohort studies (e.g.[3,6]) but little information about optimal services to support men.[1]

Recent 'game-changing' developments

Two recent developments should provide the impetus for a clearer consensus about AS. First, the ProtecT trial found no difference in prostate cancer mortality between active monitoring (AM), radiotherapy and surgery at a median of 10 years' follow-up, but metastases were found in twice as many men in the AM group (6%) compared with surgery and radiotherapy (3%) - the first robust comparative evidence about outcomes of a surveillance approach.[7,8] Second, the PRECISION trial demonstrated that pre-biopsy multiparametric MRI (mpMRI) with or without targeted biopsies was more effective at reducing the detection of low-risk prostate cancer and increasing the identification of clinically significant cancer than standard 10-12-core ultrasound-guided biopsies.[9] It is likely this will transform the diagnostic pathway.

ProtecT AM was inclusive: men with clinically localized prostate cancer were eligible for inclusion - contrasting with AS programmes restricted to men with low or very low-risk prostate cancer. ProtecT AM comprised low intensity monitoring based on PSA kinetics, with any concerns raised by patient or clinician at

any time leading to a review that could include re-evaluation of cancer status and then continuing on AM or changing to a radical option - contrasting with AS programmes with regular repeat-biopsy. After a median of two years, 20% allocated to ProtecT AM had changed to a radical option (50% at a median of 10-years)[7] - a level of change consistent with AS programmes with repeat-biopsy.

A misconception has arisen that the ProtecT trial cohort included mostly low or very low-risk prostate cancer because 75% had Gleason score 6 and 76% T1c tumours,[10] but combining PSA, T-stage and Gleason score, only two-thirds had true low-risk cancer. ProtecT was under-staged: 29% who had surgery had stage pT3 disease; it can be assumed that a similar proportion with extra-capsular disease was in the AM group. ProtecT employed a 10-core TRUS-guided biopsy protocol (without mpMRI, which was then unavailable). Men undergoing ProtecT AM thus harboured considerably more higher stage and intermediate- and high-risk cancer than was apparent from their diagnostic information. Yet their risk of death from prostate cancer over a median of 10 years was extremely low and some with intermediate-risk cancer did not progress on AM.

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The evidence presented above does not negate the AS approach for men with clinically localised prostate cancer. Far from it - cohort studies showing low risks of progression and death, the potential for more accurate diagnosis with mpMRI according to PRECISION, increasing understanding of the genomics and biological behaviour of prostate cancer, and the ProtecT results all confirm the importance and viability of AS/AM approaches. While the ProtecT AM protocol cannot be implemented because of the increased risk of metastases, many of today's AS programmes are also inappropriate, particularly those restricted only to patients with very low-risk disease and including numerous repeat-biopsies with risks of infection and lack of targeting.

There is thus a need for a 'radical' re-think about AS/AM in terms of patient inclusion, monitoring strategies, and triggers for change to radical treatment that maintain men within the 'window of curability'. Using recent evidence, clinicians can have more confident and open discussions about management options with patients diagnosed with low- and intermediate-risk prostate cancer. Men do not need to rush to choose a treatment; there is time to consider their wishes and perspectives in relation to the evidence about the effectiveness and impact of each of the major options. Some men may wish to avoid the risk of metastases at all costs and opt for surgery or radiotherapy immediately or a strict AS protocol with frequent testing, including repeat-biopsies. Others may be willing to accept a risk of progression if they are able to have less frequent and invasive monitoring that enables them to continue living their everyday lives.

New protocols need to be developed to support men on AS/AM, and their families, over many years. Lessons can be learned from the management of chronic health conditions such as arthritis - developing standardized guidelines for clinicians and supportive information for patients – as suggested in this month's article.[1]

The time is right to review existing AS/AM programmes. We need to build a new evidence-based consensus to ensure that as many men as possible can avoid unnecessary treatment while those who do need it receive radical interventions. In addition, why not also consider reducing widespread PSA testing and implement more accurate diagnostic techniques to protect men from being diagnosed with low-risk prostate cancer in the first place?

[1,000 words]

References

1. Kinsella N, Stattin P, Cahill D et al. Factors influencing men's choice of and adherence to active surveillance for low-risk prostate cancer: a mixed method systematic review. European Urology (in press).

2. Simpkin AJ, Tilling K, Martin RM et al. Systematic review and meta analysis of factors determining change to radical treatment in active surveiallance for localised prostate cancer. European Urology 2015; 67, 6: 993-1005.

3. Klotz L, Vesprini D, Sethukavalan P et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. Journal of Clinical Oncology 2014; 33,3: 272-276.

4. Donovan JL, Mills N, Smith M et al. Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ* 2002; 325: 766-770.

5. Albertsen PC, Hanley JA, Fine J. 20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer. *JAMA.* 2005;293(17):2095–2101.

6. Godtman R A, Holmberg E, Khatami A. et al. Long-term results of active surveillance in the Goteborg randomized, population-based prostate cancer screening trial. European Urology 2016 70, 5: 760–766.

7. Hamdy, F. C., Donovan, J.L., Lane, A et al, for the ProtecT Study Group. Mortality and Clinical Outcomes at 10 years' Follow-up in the ProtecT Trial. The New England Journal of Medicine. 2016; 375, 15: 1415-1424.

8. Donovan, J.L., Hamdy, F. C., Lane, A et al for the ProtecT Study Group. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. New England Journal of Medicine. 2016; 375, 15: 1425-1437.

9. Kasivisvanathan V, Rannikko AS, Borghi M et al for the PRECISION Study Group Collaborators. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. NEJM, March 19, 2018 DOI: 10.1056/NEJMoa1801993

10. Lane, J. A., Donovan, J. L., Davis, M., et al for the ProtecT study group. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncology. 2014; 15, 10: 1109-18.

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