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Best practice in active surveillance for men with prostate cancer: a Prostate Cancer UK consensus statement

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Objectives

To develop a consensus statement on current best practice of active surveillance (AS) in the UK, informed by patients and clinical experts.

Subjects and Methods

A consensus statement was drafted on the basis of three sources of data: systematic literature search of national and international guidelines; data arising from a Freedom of Information Act request to UK urology departments regarding their current practice of AS; and survey and interview responses from men with localized prostate cancer regarding their experiences and views of AS. The Prostate Cancer UK Expert Reference Group (ERG) on AS was then convened to discuss and refine the statement.

Results

Guidelines and protocols for AS varied significantly in terms of risk stratification, criteria for offering AS, and protocols for AS between and within countries. Patients and healthcare professionals identified clinical, emotional and process needs for AS to be effective. Men with prostate cancer wanted more information and psychological support at the time of discussing AS with the treating team and in the first 2 years of AS, and a named healthcare professional to discuss any questions or concerns they had. The ERG agreed 30 consensus statements regarding best practice for AS. Statements were grouped under headings: 'Inclusion/Exclusion Criteria'; 'AS follow-up protocol' and 'When to stop AS'.

Conclusion

Significant variation currently exists in the practice of AS in the UK and internationally. Men have clear views on the level of involvement in treatment decisions and support from their treating professionals when receiving AS. The Prostate Cancer UK AS ERG has developed a set of consensus statements for best practice in AS. Evidence for best practice in AS, and the use of multiparametric magnetic resonance imaging in AS, is still evolving, and further studies are needed to determine how to optimize AS outcomes.

Keywords

active surveillance, clinical consensus, guidelines, #PCSM, #ProstateCancer, #uroonc

Introduction

Prostate cancer incidence in high-income countries, including the UK, has increased by up to 300% in recent decades, while prostate cancer mortality has remained largely static [1]. The rise in incidence has been largely driven by the detection of more early-stage and indolent cancers, and the ageing population [2].

Active surveillance (AS) has evolved as a viable approach for some men with prostate cancer, and involves regular monitoring for signs of cancer progression in patients with low- to intermediate-risk, localized prostate cancer, in order to defer or avoid radical treatment [3]. Recent studies, such as PROTECT and PIVOT, have shown no difference in 10-year mortality between patients receiving radical treatment and those undergoing monitoring, although it should be

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noted that the monitoring in these studies differed from modern AS practice [4,5].

Men with low-risk prostate cancer, and some men with intermediate-risk prostate cancer, are encouraged to consider AS after initial diagnosis. In the UK, the uptake of AS for low-risk prostate cancer has increased with the publication of the 2008 National Institute for Health and Care Excellence (NICE) guidelines recommending AS as the preferred option for men with low-risk prostate cancer [6,7]. The latest publication from the National Prostate Cancer Audit suggests that the rate of potential overtreatment reduced from 12% in April 2014 to March 2015 compared with 8% in April 2015 to March 2016 [8]. Perceptions about treatment efficacy and side effects are important factors for men in deciding between management options [9]. Despite variation in AS protocols and inclusion criteria, meta-analyses and systematic reviews have suggested a higher prevalence of anxiety in men undergoing AS compared to the general population [10,11]. Provision of extra information and psychological support for men on AS have consistently been highlighted as areas of need for improvement [9,12–14]. There is a scarcity of literature on the subject of AS, and studies tend not to reflect current UK practice.

Active surveillance clinical guidelines and implementation of AS varies between and within countries [15]. The 'Movember'-funded Global Action Project 3 on Active Surveillance (GAP3) has the largest pooled cohort of men on AS, incorporating over 14 000 patients across 25 centres worldwide [16]. GAP3 aims to use the data gathered from this cohort to inform AS guidelines internationally on the selection and monitoring of patients with low-risk prostate cancer. The group has also published an expert consensus document on the semantics used in AS, to facilitate international discussion [17].

Multiparametric MRI (mpMRI) is established in the UK as a useful tool to aid prostate cancer diagnosis, and it is recommended in the 2014 NICE guidelines for the assessment of men, both early in surveillance, and during follow-up [18]. The exact role of mpMRI in AS is under discussion, including the possibility that it can be used to avoid repeat biopsies in some men [19–21]. Trials with long-term follow-up incorporating mpMRI within AS protocols, such as the SPCG17: Prostate Cancer Active Surveillance Trigger Trial (clinicaltrials.gov identifier NCT02914873), are ongoing.

Prostate Cancer UK commissioned the present research to develop an in-depth understanding of current AS practice for men with prostate cancer, to inform discussions around the role of AS in the treatment pathway for localized prostate cancer, and to define current best practice in AS in the UK.

Subjects and Methods

The present consensus statement was informed by a systematic literature search of current national and international guidelines and protocols. These were analysed for commonality of practice, thresholds for inclusion, follow-up intensity and triggers used to switch men to radical treatment, whether surgery or radiotherapy. A Freedom of Information Act request to urology departments across the UK regarding their current practice of AS was submitted in July 2017 and included questions about each department's AS protocol, inclusion criteria for AS, use of mpMRI at diagnosis and follow-up for men on AS. A PubMed literature search for AS protocols incorporating mpMRI was also performed.

Men with localized prostate cancer were recruited through self-selection to complete an online survey of their experiences and views of AS via Prostate Cancer UK social media accounts, prostate cancer support groups, volunteer networks and direct email invitations. Prostate Cancer UK staff and expert patients developed the questionnaire content (Appendix S1). Quantitative survey data obtained were analysed using descriptive statistics. In-depth, qualitative interviews of men with prostate cancer on AS and men without prostate cancer were undertaken to further understand their views and experiences of AS. Interviewees were recruited using a qualitative market research fieldwork agency (*Criteria*), using a screener questionnaire. In-depth interviews were expanded to include clinicians and academics with expertise in prostate cancer and AS.

A set of consensus statements on the best practice approach to AS, incorporating mpMRI, was developed based on existing guidelines, protocols used by UK Urology departments, and survey data from men with localized prostate cancer. The views and experiences of men were also used to develop consensus statements to address the support and information needs of men during diagnosis, treatment decision-making and during AS follow-up. The draft consensus statements were then discussed at a face-to-face meeting of a subgroup of the Prostate Cancer UK Active Surveillance Expert Reference Group (ERG). The full ERG consisted of 27 members, selected because of their peer-reviewed publications and expertise in prostate cancer diagnosis, and/or AS inclusion and management. This group worked virtually to support the research and development of draft clinical consensus statements. Membership covered the following professions and backgrounds: urology; oncology; radiology; pathology; general practice; clinical specialist nursing; clinical psychology; research; patient experts; and representatives from relevant professional bodies – the BAUS, British Association of Urological Nurses, Royal College of Radiologists, Royal College of Pathologists and Royal College of General Practitioners. A subgroup of the ERG (ERG Panel) consisting of 14 members (12 clinicians and two patient

experts) was convened on 8 March 2018 for a further round of review of the consensus statements. The ERG Panel included three urologists, two pathologists, two radiologists, two GPs, one expert patient, one patient group representative, one uro-oncology clinical nurse specialist, one urology advanced nurse practitioner, and one researcher. The panel was chaired and observed by representatives from Prostate Cancer UK. The ERG Panel reviewed evidence, discussed the draft consensus statements and agreed on the final clinical consensus statement.

Results

Active Surveillance Guidelines

International guidelines for AS were identified from the UK, Europe, Canada and North America. These guidelines demonstrated variation in a number of key areas. In terms of risk stratification, the guidelines included different risk categories and used different key clinical characteristics to determine a patient's risk. mpMRI was only addressed in half of the guidelines identified, and recommendations for using mpMRI varied greatly. NICE guidance and the Canadian Urological Association guidelines were the only two to consider recommending AS to patients with intermediate-risk prostate cancer. Protocols for AS follow-up also showed significant heterogeneity in terms of frequency of follow-up and PSA testing, use of mpMRI and whether to perform surveillance biopsies (Table 1).

Freedom of Information Request

A total of 92.4% of acute hospital trusts, health boards, and health and social care boards (145/157) in the UK responded to the Freedom of Information request. Of these 145 providers, 58 (40.0%) stated that they followed current NICE guidance (Prostate cancer: diagnosis and management Clinical guideline [CG175]), and 48.3% (70/145) either followed an adapted version of NICE guidance or a local protocol. Ten providers (6.9%) stated they had no protocol in place, and 3.4% (5/145) followed an alternative external protocol.

The most commonly cited factors in assessing men for AS suitability were PSA level, clinical stage and Gleason score, although there was large variability among providers in the upper limit for clinical stages deemed suitable for AS (T1–T2C). Variability also occurred in utilization of family history and ethnicity as inclusion criteria. Of the trusts who provided an answer for these questions, 50.8% of providers (62/122) stated that family history was used as a separate inclusion criterion, whereas 40.2% of providers (49/122) did not use family history to decide AS suitability. A total of 60.5% of providers (72/119) responded that black ethnicity was used as an inclusion criterion to determine AS suitability. Furthermore, 68.6% of providers (83/121) stated that calendar age was used as an inclusion criterion, and 83.3% of providers (90/108) used life expectancy to determine AS suitability. Use of mpMRI, biopsy and re-biopsy methods also varied, but this could potentially be a result of shifting UK practices.

Patient Survey

A total of 744 men with prostate cancer from across the UK completed the online survey; 619 (83.2%) of these men had been diagnosed with localized disease. Of those who answered the screening questions 95.8% (362/378) were white British, and 70.6% (267/378) were diagnosed between the ages of 55–69 years. Approximately 40% of patients diagnosed over the last 5 years did not recall being presented with AS as a treatment option. Of the survey respondents who had received AS as a treatment, 62.0% (163/263) were still on an AS treatment programme, whilst 27.8% (73/263) of survey respondents had left AS as a result of cancer progression, and 8.0% (21/263) through patient choice.

Concerns about the risk of developing metastases (73.7% [202/274]) outweighed the ability to avoid/delay treatment to avoid side effects (47.0% [118/251]) for men faced with the option of undergoing AS. 'Discussion with a specialist about AS' (72.3% [289/400]), 'Access to test results and explanations of the results' (70.3% [281/400]), and 'A named healthcare professional to discuss any questions or concerns' (66.3% [265/400]) were the most commonly selected options for what should be available for men on AS.

Interviews with Patients, Clinicians and Academics

Twelve face-to-face and eight telephone interviews were conducted with a range of relevant stakeholders, including men with and without prostate cancer and healthcare professionals with expertise in AS. Patients and healthcare professionals identified clinical, emotional and process needs for AS to be effective. The initial consultation explaining the diagnosis and treatment options appeared to be crucial for men's opinion of AS. Men with prostate cancer wanted more objective information and emotional support at the time of discussing AS with the treating team and in the first 2 years of AS. A central driver for men to choose AS was the avoidance of side effects from radical treatment and enabled them to 'play down' their cancer diagnosis, whilst, for others, AS appeared to go against the 'find it early and treat it' narrative. Continuity of care, seamless follow-up appointment bookings, and clarity on test results and trends were key themes for men with positive experiences of AS.

Consensus Statement

The panel agreed a consensus statement regarding the best practice approach to AS. Statements were grouped under headings: 'Inclusion/Exclusion criteria'; 'AS follow-up

Table 1 International guidelines for active surveillance.

	Risk stratification	Inclusion	AS protocol – Year 1	AS protocol – Year 2+	Switch to radical treatment criteria
NICE [22]	PSA <10 ng/mL AND Gleason score ≤6 AND Clinical stage T1–T2a	Low-risk Consider in intermediate-risk, localized tumours.	PSA every 3–4 months Monitor PSA kinetics throughout AS DRE every 6–12 months Repeat TRUS biopsy at 12 months	PSA every 3–6 months Monitor PSA kinetics throughout AS DRE every 6–12 months	Evidence of progression, in light of patient preferences, comorbidities and life expectancy
BAUS [29]	PSA <10 ng/mL Gleason score ≤6 Clinical T-stage T1–T2 <50% positive biopsy cores	Low-risk and low-volume intermediate-risk	PSA, MRI ± TRUS biopsy at 3-month review Further review after 6–12 months Repeat mpMRI at 12 months	Regular PSA blood test Review every 12 months Repeat mpMRI and biopsy every 2–4 years	Re-investigate or progress to radical treatment if: significant PSA rise; changes on DRE or MRI; change in patient preference; increased tumour volume or grade on repeat biopsy
AUA [30]	PSA <10 ng/mL Grade group 1 (Gleason ≤6) Clinical stage T1–T2a	Low-risk Intermediate-(favourable) risk	PSA every 3 months DRE at review Repeat TRUS biopsy within 2 years Consider mpMRI	PSA every 3–6 months DRE at review Surveillance biopsies	Adverse reclassification Growth of lesion on mpMRI Increased PSA density
National Comprehensive Cancer Network [31]	PSA <10 ng/mL Gleason score ≤6 Clinical stage T1–T2a	Low-risk	PSA >6 monthly DRE >12 monthly Repeat TRUS biopsy >12 monthly Consider mpMRI if signs of progression	PSA >6 monthly DRE >12 monthly Repeat biopsy >12 monthly Consider mpMRI if signs of progression	Changes on repeat biopsy; Gleason score 4 or 5 Increased number of positive cores Increased tumour length in core
Cancer Care Ontario [32]		Low-risk	PSA every 3–6 months DRE every 12 months TRUS biopsy within 6–12 months	PSA every 3–6 months DRE every 12 months Serial biopsy every 3–5 years	Consider if repeat biopsy shows; Gleason score >6 Significant increase in Gleason score 6 volume
Canadian Urological Association[23]	PSA <10 ng/mL Gleason score ≤6 Clinical stage ≤2a	Low-risk. Consider in intermediate-risk, localized tumour	PSA every 3–6 months DRE every 12 months TRUS biopsy within 6–12 months	PSA every 3–6 months DRE every 12 months Serial biopsy every 3–5 years	Consider if repeat biopsy shows; Gleason score >6 Significant increase in Gleason score 6 volume
European Association of Urology [33]	PSA <10 ng/mL Gleason score ≤6 Clinical stage T1–T2a	Low-risk	Follow-up based on PSA, DRE and repeat TRUS biopsy. Optimal interval is unclear.	Follow-up based on PSA, DRE and repeat biopsy. Optimal interval is unclear.	No agreement currently. Possible criteria include: change in Gleason score; increased positive cores or lengths of cores; T-stage increase; PSA changes; change in patient preferences
PRIAS [34]	Clinical stage T1c/T2 PSA ≤10 ng/mL PSA density <0.2 ng/mL per mL 1–2 positive cores Gleason score ≤6	Low-risk	PSA every 3 months Repeat TRUS biopsy at 12 months	PSA every 3 months until 2 years, then every 6 months Repeat TRUS biopsies after 4 and 7 years, or annually up to 10 years if PSA doubles	Three or more positive biopsies and/or Gleason score >6

AS, active surveillance; mpMRI, multiparametric MRI; NICE, National Institute for Health and Care Excellence; PRIAS, Prostate Cancer Research International: Active Surveillance.

protocol' and 'When to stop AS'. The full list of consensus statements can be found in Table 2.

Discussion

The Prostate Cancer UK Active Surveillance ERG assessed data from a review of international AS guidelines, a Freedom of Information request to UK Urology departments, and quantitative and qualitative data from men with prostate cancer to inform a clinical consensus statement on the best practice of AS. This research found significant variation in current guidelines and protocols for AS in men with low- and intermediate-risk prostate cancer internationally, with variation in practice across the UK. Interviews and surveys conducted with men with prostate cancer elicited key factors in their treatment decision-making concerning AS, and identified their information and support needs for men receiving AS. Significant gaps in the literature surrounding the appropriate timing of mpMRI and other follow-up tests for men on AS were identified.

Active surveillance is increasingly being used for men with prostate cancer, in the context of rising rates of diagnosis of

Table 2 Prostate Cancer UK Expert Reference Group on active surveillance (AS) consensus statements on best practice of AS.

Inclusion criteria
Gleason score: 3 + 3 – primary treatment recommended is AS
Consider AS for men with prostate cancer with the following characteristics:
Gleason score: 3 + 4 **AND**
mpMRI T stage: ≤T2* **AND**
Biopsy and MRI should be concordant **AND**
PSA density of ≤0.2 ng/mL^2 **AND**
Men enrolled onto AS should be considered fit for radical treatment
Note: Men who are suitable for AS should have access to specialist information and support during the decision-making stage. Patient priorities should be considered, and all potential treatments, side effects and risks should be discussed prior to AS enrolment.
**For men not suitable for mpMRI, clinical T-stage should be used.*
Exclusion criteria
Men not suitable for AS include:
Gleason score ≥4 + 3 with pattern 4 disease in > 2 cores or >5 mm of cancer in a single core** **OR**
mpMRI T stage: ≥T3a*
**For men not suitable for mpMRI, clinical T-stage should be used.*
*** Very-low- volume Gleason 4 + 3 – consider re-biopsy if patient wishes to have AS. [Low volume defined as Gleason 4 pattern disease in 1 or 2 cores or <5 mm of cancer in any core.]*
AS follow-up protocol
Men on AS should have access to a clinical specialist nurse
Men should be offered and have access to support /counselling during their time on AS
Year 1 of AS
Men should be provided with a personalized AS plan, including details of PSA interval, individualized PSA threshold for re-assessment and follow-up. The personalized plan should be communicated to the patient's GP.
A repeat PSA test should be carried out in line with the recommended PSA interval and threshold† communicated by the patient's Urology Consultant within the personalized AS plan.
†*The factors that will influence a patient's PSA interval could include: PSA history; mpMRI results; and PSA density.*
If the patient's individualized PSA threshold is breached then the GP should check a mid-stream urine specimen for infection, and re-check the PSA after 6 weeks if the urine is negative for infection. If the PSA threshold remains breached, then the GP should re-refer the patient for further diagnostics.
A repeat mpMRI scan should be conducted at 12 months after baseline.
Consider deferring routine 12-month biopsy if patient is considered low risk of progression or re-classification, e.g. stable mpMRI and PSA.
A DRE should be performed at 12 months where mpMRI is contraindicated.
A repeat biopsy should be offered when mpMRI shows a suspicion of progression or if there is evidence of PSA changes (e.g. the individualized PSA threshold is breached).
Year 2+ of AS
Men should be provided with an updated personalized AS plan that should be communicated to their GP.
A repeat PSA test should be carried out in line with the recommended PSA interval and threshold† communicated by the patient's Urology Consultant within the personalized AS plan.
†*The factors that will influence a patient's PSA interval could include: PSA history; mpMRI results; and PSA density.*
If the patient's individualized PSA threshold is breached then the GP should check a mid-stream urine specimen for infection, and re-check the PSA after 6 weeks if the urine is negative for infection. If the PSA threshold remains breached, then the GP should re-refer the patient for further diagnostics.
A repeat mpMRI scan should be considered if a lesion was visible at baseline or the PSA rises and breaches the individualized PSA threshold.
A DRE should be considered on an individual basis.
A repeat biopsy should be offered when mpMRI shows a suspicion of progression.
Clinical assessment of suitability for radical treatment should be reviewed periodically.
When to stop AS
The decision to change from AS to radical treatment or watchful waiting should be made in light of the individual man's personal preferences, in addition to clinical features, comorbidities, functional impairment (i.e. e-Frailty index) and life expectancy.

AS, active surveillance; mpMRI, multiparametric MRI. The AS follow-up protocol acknowledges: that there are limitations of using PSA kinetics as a predictor of biopsy reclassification, hence, some men, especially those who are risk averse, may opt for an interval biopsy even if MRI images and PSA tests remain stable; that it is not clear, from currently available evidence, what the ideal intervals for AS follow-up should be; and that the recommended surveillance protocol remains dynamic and will respond to evolving evidence.

clinically insignificant prostate cancer [1]. Risk stratification across international guidance and local AS protocols in the UK mostly use PSA, clinical T-stage and Gleason score, with limited current use of mpMRI to varying degrees. Only two current guidelines for AS include recommendations to consider AS for some men with intermediate-risk prostate cancer [22,23]. The ERG also recommended offering AS for a subset of men with intermediate-risk prostate cancer using a strictly defined set of clinical criteria, although this may have differed if more panel members were drawn from outside the UK.

Follow-up protocols for AS is an area where there is a much greater need for clinical consistency. The use of PSA, DRE and repeat biopsy for men receiving AS varies widely. The role of mpMRI in monitoring disease progression is also an evolving field, and the evidence base is currently limited. A UK study of AS incorporating baseline biopsy, annual mpMRI, 3-monthly PSA testing, and re-biopsy at 1 and 3 years after baseline showed mpMRI changes were the main trigger for detecting prostate cancer progression, but per-protocol re-biopsy also detected changes not picked up by mpMRI or PSA [24]. A scarcity of quality AS treatment trials and agreed international approaches hampered the development of clear clinical consensus by the ERG.

In an attempt to fill the evidence void for best practice in AS, the ERG made some patient-centred and innovative recommendations for AS where consensus could be reached (Table 2). A personalized AS plan specifying PSA frequencies and thresholds for re-investigation, should be developed by the treating urologist taking into account individual patient factors (e.g. age, comorbidities) and their previous total PSA and PSA density. This plan then needs to be shared with the patient and their GP to ensure all parties are clear on the individualized approach to AS for the patient. There is a strong emphasis on providing men who are offered AS with specialist information and support through the decision-making process.

This process to develop and agree clinical consensus statements on best practice for AS was informed by a wide range of data sources, bringing together the evidence from national guidelines, expert opinion and, crucially, the views of men with prostate cancer. Incorporating patient's views on AS through multiple triangulated sources (surveys, interviews and ERG participation) adds to the strength of the consensus statements [25]. This robust evidence base was employed to draft the clinical statements, which were then interrogated and debated by experts in the field to achieve consensus.

The major limitation of the present research is the lack of high-quality, large multicentre studies on which to base the consensus statements regarding the utility of mpMRI in AS risk stratification and follow-up, the optimal frequency of mpMRI, and thresholds/triggers for biopsy or treatment for men on AS. The aim of the GAP3 cohort study is to provide useful insights into the selection and monitoring of men for AS, and the PRECISE recommendations give a framework for reporting MRI in AS to aid data collection in future studies [26]. Consensus was not reached amongst the ERG on a specified frequency of repeat biopsy for men on AS, but it was agreed that this could be informed by evidence of change in PSA or mpMRI findings. This approach could potentially miss some tumours, as highlighted in the PROMIS [27] and PROTECT [4] trials, but has also been recommended in the recently published draft update of NICE guidance [28].

Significant variation currently exists in AS internationally and within the UK. Men have clear views on their level of involvement in treatment decisions and on support from their treating professionals if they are undergoing AS. The Prostate Cancer UK Active Surveillance ERG has developed a set of consensus statements to try and guide standards for AS going forward. Evidence for best practice in AS is still evolving. Information and support needs for men receiving AS must be clearly understood, and further prostate cancer treatment trials are needed to determine how to optimize AS outcomes.

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Conflict of Interest

None declared.

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Abbreviations: AS, active surveillance; ERG, Expert Reference Group; NICE, National Institute for Health and Care Excellence; GAP3, Global Action Project 3 on Active Surveillance.

Supporting Information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Questions for Survey [Monkey] to men with experience of prostate cancer.