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Review – Prostatic Disease – Editor's Choice

EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study)

Thomas B.L. Lam [a,b,†,], Steven MacLennan [a,†], Peter-Paul M. Willemse [c], Malcolm D. Mason [d], Karin Plass [e], Robert Shepherd [e], Ruud Baanders [f], Chris H. Bangma [g], Anders Bjartell [h], Alberto Bossi [i], Erik Briers [j], Alberto Briganti [k], Karel T. Buddingh [l], James W.F. Catto [m,n], Maurizio Colecchia [o], Brett W. Cox [p], Marcus G. Cumberbatch [m], Jeff Davies [q], Niall F. Davis [r,s], Maria De Santis [t], Paolo Dell'Oglio [u,v], André Deschamps [w], James F. Donaldson [a,b], Shin Egawa [x], Christian D. Fankhauser [y], Stefano Fanti [z], Nicola Fossati [aa], Giorgio Gandaglia [u], Silke Gillessen [aa,bb], Nikolaos Grivas [cc], Tobias Gross [dd], Jeremy P. Grummet [ee], Ann M. Henry [ff], Alexandre Ingels [gg], Jacques Irani [hh], Michael Lardas [ii], Matthew Liew [jj], Daniel W. Lin [kk,ll], Lisa Moris [mm,nn], Muhammad Imran Omar [a], Karl H. Pang [m], Catherine C. Paterson [a,oo,pp], Raphaële Renard-Penna [qq], Maria J. Ribal [rr], Monique J. Roobol [g], Morgan Rouprêt [ss], Olivier Rouvière [tt,uu], Gemma Sancho Pardo [vv], Jonathan Richenberg [ww], Ivo G. Schoots [xx], J.P. Michiel Sedelaar [yy], Phillip Stricker [zz,aaa], Derya Tilki [bbb,ccc], Susanne Vahr Lauridsen [ddd], Roderick C.N. van den Bergh [eee], Thomas Van den Broeck [mm], Theodorus H. van der Kwast [fff], Henk G. van der Poel [cc], Geert J.L.H. van Leenders [fff], Murali Varma [ggg], Philippe D. Violette [hhh], Christopher J.D. Wallis [iii,jjj], Thomas Wiegel [kkk], Karen Wilkinson [lll], Fabio Zattoni [mmm], James M.O. N'Dow [a,b], Hendrik Van Poppel [mm], Philip Cornford [nnn], Nicolas Mottet [ooo]*

[a] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [b] *Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK;* [c] *Department of Urology, University Utrecht, Utrecht, The Netherlands;* [d] *Division of Cancer and Genetics, School of Medicine Cardiff University, Velindre Cancer Centre, Cardiff, UK;* [e] *EAU Guidelines Office, Arnhem, The Netherlands;* [f] *Oxford, UK;* [g] *Department of Urology, Erasmus University Medical Centre, Rotterdam, The Netherlands;* [h] *Department of Urology, Skåne University Hospital Malmö, Lund University, Lund, Sweden;* [i] *Department of Radiation Oncology, Gustave Roussy Institute, Villejuif, France;* [j] *Hasselt, Belgium;* [k] *Department of Urology, Scientific Institute and University Vita-Salute San Raffaele Hospital, Milan, Italy;* [l] *HagaZiekenhuis, The Hague, The Netherlands;* [m] *Academic Urology Unit, University of Sheffield, Sheffield, UK;* [n] *Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK;* [o] *Uropathology Unit, Department of Pathology, Fondazione Ircss Istituto Nazionale dei Tumori di Milano, Milan, Italy;* [p] *Department of Radiation Medicine, Zucker School of Medicine, Hempstead, New York, NY, USA;* [q] *Wales, UK;* [r] *Department of Urology, Beaumont and Connolly Hospitals, Dublin, Ireland;* [s] *Royal College of Surgeons in Ireland, Dublin, Ireland;* [t] *Department of Urology, Charité University Hospital, Berlin, Germany;* [u] *Unit of Urology, Division of Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy;* [v] *ORSI Academy, Melle, Belgium;* [w] *Europa Uomo, Antwerp, Belgium;* [x] *Asian School of Urology, UAA, Jikei University School of Medicine, Tokyo, Japan;* [y] *Department of Urology, University of Zurich, Zurich, Switzerland;* [z] *Department of Nuclear Medicine, Policlinico S.Orsola, University of Bologna, Italy;* [aa] *Division of Cancer Sciences, University of Manchester and The Christie, Manchester, UK;* [bb] *Department of Medical Oncology and Haematology, Cantonal Hospital St. Gallen,*

[†] These authors are joint first authors.
[*] Corresponding author. Academic Urology Unit, University of Aberdeen, 2nd Floor, Health Sciences Building, Foresterhill, Aberdeen AB25 2ZD, UK. Tel. +44 1224 438130; Fax: +44 1224 550726.
E-mail addresses: thomas.lam@nhs.net, thomasbllam@abdn.ac.uk (Thomas B.L. Lam).

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University of Bern, Bern, Switzerland; [cc] *Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands;* [dd] *Department of Urology, University of Bern, Bern, Switzerland;* [ee] *Department of Surgery, Central Clinical School, Monash University, Melbourne, Australia;* [ff] *Leeds Cancer Centre, St. James's University Hospital, Leeds, UK;* [gg] *Department of Urology, Henri Mondor Hospital, Créteil, France;* [hh] *University Hospital of Bicêtre—Paris Sud—Saclay University, Le Kremlin Bicêtre, France;* [ii] *Department of Reconstructive Urology and Surgical Andrology, Metropolitan General, Athens, Greece;* [jj] *Department of Urology, Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, UK;* [kk] *Cancer Prevention Program, Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA;* [ll] *Department of Urology, University of Washington, Seattle, WA, USA;* [mm] *Department of Urology, University Hospitals Leuven, Leuven, Belgium;* [nn] *Laboratory of Molecular Endocrinology, KU Leuven, Leuven, Belgium;* [oo] *University of Canberra, School of Nursing, Midwifery and Public Health, Canberra, Australia;* [pp] *Robert Gordon University, School of Nursing and Midwifery, Aberdeen, UK;* [qq] *Academic Department of Radiology, Sorbonne Université, GRC no 5, ONCOTYPE-URO, AP-HP, Hôpital Pitié-Salpêtrière-Hôpital Tenon, Paris, France;* [rr] *Uro-Oncology Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain;* [ss] *Urology Department, Sorbonne Université, GRC ndeg5, ONCOTYPE-URO, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France;* [tt] *Hospices Civils de Lyon, Department of Urinary and Vascular Imaging, Hôpital Edouard Herriot, Lyon, France;* [uu] *Université de Lyon, Université Lyon 1, Faculté de Médecine Lyon Est, Lyon, France;* [vv] *Department of Radiation Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [ww] *Royal Sussex County Hospital Brighton and Brighton and Sussex Medical School, Brighton, Sussex, UK;* [xx] *Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands;* [yy] *Department of Urology, Radboud University Medical Centre, Nijmegen, The Netherlands;* [zz] *Department of Urology, St Vincents Hospital and Campus, Sydney, Australia;* [aaa] *Garvan Institute of Research, Sydney, Australia;* [bbb] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [ccc] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [ddd] *Department of Urology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark;* [eee] *Department of Urology, St. Antonius Hospital, Utrecht, The Netherlands;* [fff] *Department of Pathology, Erasmus MC University Medical Center, Rotterdam, The Netherlands;* [ggg] *Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK;* [hhh] *Departments of Health Research Methods, Evidence and Impact (HEI) and Surgery, McMaster University, Hamilton, ON, Canada;* [iii] *Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada;* [jjj] *Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA;* [kkk] *Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany;* [lll] *University College London Hospitals, London, UK;* [mmm] *Urology Unit, Academic Medical Centre Hospital, Udine, Italy;* [nnn] *Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK;* [ooo] *Department of Urology, University Hospital, St. Etienne, France*

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Abstract

Background: There is uncertainty in deferred active treatment (DAT) programmes, regarding patient selection, follow-up and monitoring, reclassification, and which outcome measures should be prioritised.
Objective: To develop consensus statements for all domains of DAT.
Design, setting, and participants: A protocol-driven, three phase study was undertaken by the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Association of Urology Section of Urological Research (ESUR)-International Society of Geriatric Oncology (SIOG) Prostate Cancer Guideline Panel in conjunction with partner organisations, including the following: (1) a systematic review to describe heterogeneity across all domains; (2) a two-round Delphi survey involving a large, international panel of stakeholders, including healthcare practitioners (HCPs) and patients; and (3) a consensus group meeting attended by stakeholder group representatives. Robust methods regarding what constituted the consensus were strictly followed.
Results and limitations: A total of 109 HCPs and 16 patients completed both survey rounds. Of 129 statements in the survey, consensus was achieved in 66 (51%); the rest of the statements were discussed and voted on in the consensus meeting by 32 HCPs and three patients, where consensus was achieved in additional 27 statements (43%). Overall, 93 statements (72%) achieved consensus in the project. Some uncertainties remained regarding clinically important thresholds for disease extent on biopsy in low-risk disease, and the role of multiparametric magnetic resonance imaging in determining disease stage and aggressiveness as a criterion for inclusion and exclusion.
Conclusions: Consensus statements and the findings are expected to guide and inform routine clinical practice and research, until higher levels of evidence emerge through prospective comparative studies and clinical trials.
Patient summary: We undertook a project aimed at standardising the elements of practice in active surveillance programmes for early localised prostate cancer because currently there is great variation and uncertainty regarding how best to conduct them. The project involved large numbers of healthcare practitioners and patients using a survey and face-to-face meeting, in order to achieve agreement (ie, consensus) regarding best practice, which will provide guidance to clinicians and researchers.

1. Introduction

Deferred treatment with curative intent (ie, deferred active treatment [DAT]) has emerged as a feasible alternative to standard radical interventions for low-risk localised prostate cancer [1–3]. This includes active surveillance or active monitoring, whereby patients are not curatively treated immediately but instead are reassessed and monitored at regular intervals, and involves a choice by a patient following counselling with their physician, and alternative treatment options may be considered at a future time point. Large, prospective studies are currently underway, and medium-term outcomes appear to be promising [4,5]. However, clinical practice guidelines (CPGs) [6] often acknowledge the significant heterogeneity inherent in deferred treatment strategies, with protocols differing in patient eligibility, selection and recruitment, disease monitoring and reassessment, outcome definition and measurement, and triggers for reclassification and change in management. In short, there is uncertainty regarding the definition of eligible patients and the optimum follow-up strategies. Although attempts have been made to standardise definitions and terminology via consensus methods [7], there have been no successful projects that harness clinical and patient expertise aiming to standardise practice comprehensively.

Consequently, the European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Association of Urology Section of Urological Research (ESUR)-International Society of Geriatric Oncology (SIOG) Prostate Cancer Guideline Panel in conjunction with partner organisations (Supplementary material) commissioned and undertook a project to develop consensus statements for DAT. The project was unique and novel in its use of protocol-driven consensus methods [8]. The specific objectives were to achieve consensus on the following domains: (1) criteria for patient selection, inclusion, and exclusion; (2) nature and timing of investigations and assessments during monitoring and follow-up; (3) criteria and thresholds for reclassification and change in management; and (4) type of outcome measures that should be prioritised. The study findings will be incorporated into international CPGs issued by the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel and collaborators, and will guide and inform clinical practice and further research.

2. Material and methods

The protocol outlining the detailed methods underpinning the project has been published [8]. An overview of the study is depicted in Fig. 1. The project was divided into three phases, lasting 12 mo. Phase 1 was a systematic review of current DAT practice [9], the results of which are summarised in Tables 1–4 and the Supplementary material. The review

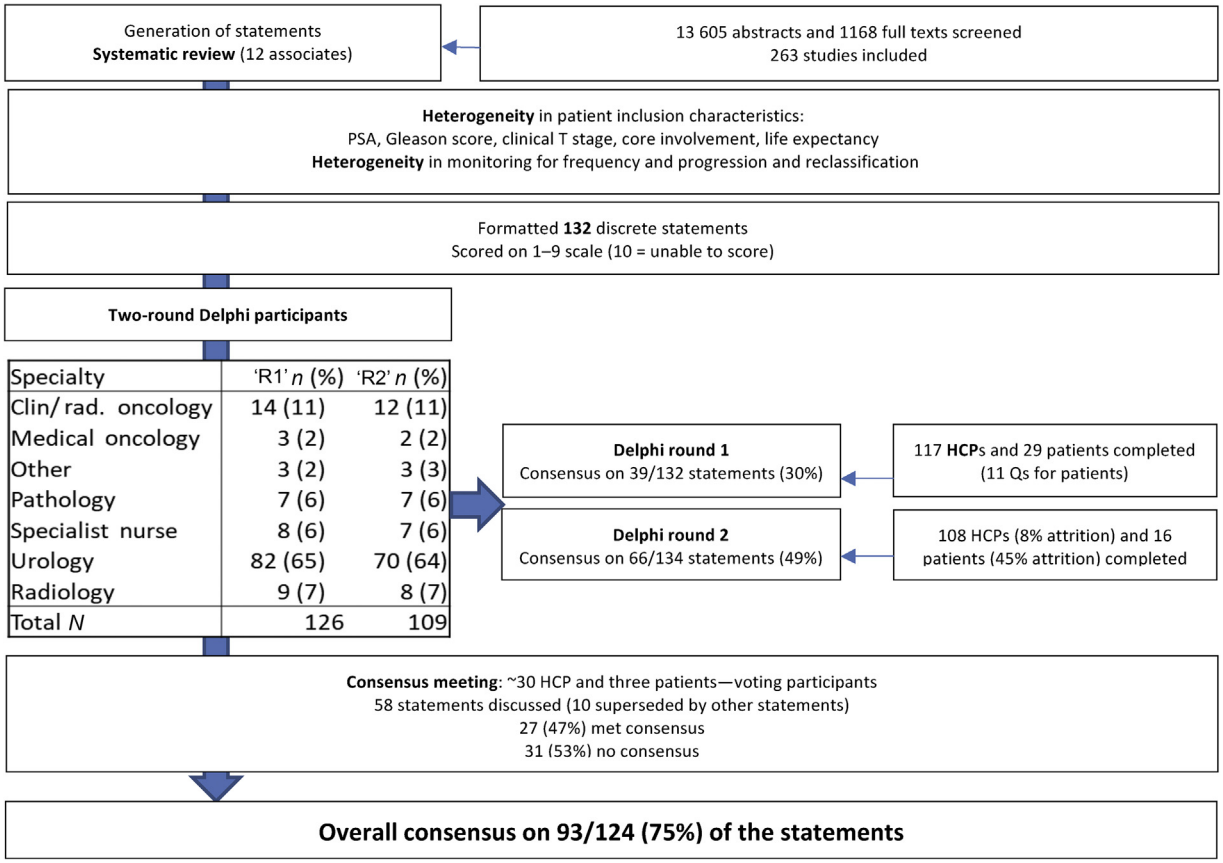


Fig. 1 – Flow chart summarising study.
Clin = clinical; HCP = healthcare professional; *N* = number; PSA = prostate-specific antigen; Q = question; rad. = radiation; R1 = round 1; R2 = round 2.

Table 1 – Summary of systematic review findings (total *n* = 282 studies): criteria within the domains of inclusion, monitoring, reclassification, and outcome measures.

Domains	No. of different definitions	No. of studies providing definition for this criterion
Main criteria for inclusion to DAT		
PSA cut-off	13	251
Gleason sum score	13	282
Clinical T stage	14	275
Number of positive cores	12	270
Core involvement per core	11	270
PSA density	9	265
Monitoring and follow-up characteristics during DAT		
PSA testing frequency	23	193
DRE frequency	26	157
TRUS rebiopsy frequency	32	197
Number of cores taken	29	122
mpMRI frequency	24	74
Reclassification characteristics during DAT		
Clinical T stage	13	89
Gleason sum score	13	202
PSA doubling time	5	86
Number of positive cores	13	147
Core involvement per core	8	122
Patient preference	2	58
Types of outcomes measured		
Quality of life	6	81
Sexual function	3	75
Survival outcome	3	114
Disease-specific outcome	15	221

DAT = deferred active treatment; DRE = digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; No. = number; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

Table 2 – Summary of systematic review findings: most common combinations of inclusion criteria for DAT.

PSA level	Gleason score	Clinical T category	No. of positive cores	Core involvement (%)	PSA density	No. of studies
≤10	≤3 + 3	T1c-T2c	≤2	NR	<0.2	34
NR	≤3 + 3	T1c	≤2	<50	<0.15	13
≤10	≤3 + 3	≤T2a	≤3	≤50	NR	9
NR	≤3 + 3	NR	NR	NR	NR	7
≤10	≤3 + 3	≤T2c	≤2	NR	≤ 0.2	5
≤15	≤7	T1b-T2b	NR	NR	NR	5
<15	≤3 + 3	≤T2a	≤2	NR	NR	5
NR	≤3 + 3	≤T2a	≤2	≤20	NR	4

DAT = deferred active treatment; NR = not recorded; PSA = prostate-specific antigen.

Table 3 – Summary of systematic review findings: most common combination of monitoring and follow-up characteristics during DAT.

PSA frequency	DRE frequency	TRUS rebiopsy frequency	Number of cores taken	mpMRI frequency	No. of studies
6/12	6/12	12/12	Multiple	Multiple	24
6/12	6/12	Multiple	Multiple	Multiple	18
3/12 for 2 yrs 6/12 thereafter	3/12 for 2 yr 6/12 thereafter	Multiple	Multiple	NR	11
3/12	6/12	Multiple	Multiple	NR	9
3/12 for 2 yr 6/12 thereafter	6/12 for 2 yr 12/12 thereafter	Multiple	Multiple	Multiple	6
3/12 1 st yr 6/12 thereafter	3/12 1 st yr 6/12 thereafter	Multiple	Multiple	NR	6
6/12	NR	12/12	Multiple	Multiple	6
3/12	3/12	12/12	NR	NR	5
3/12 1 st yr 6/12 thereafter	Multiple	Multiple	Multiple	NR	5
6–12/12	6–12/12	Multiple	Multiple	Multiple	5

DAT = deferred active treatment; DRE = digital-rectal examination; mpMRI = multiparametric magnetic resonance imaging; NR = not recorded; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

findings were used to inform a list of statements, and organised into domains and subdomains reflecting the aspects of DAT (ie, patient eligibility and recruitment, follow-up and monitoring, reclassification, and outcome measures).

In phase 2, the list of statements was incorporated into an online questionnaire as part of a two-round iterative Delphi survey. An international panel of participants including healthcare practitioners (HCPs; ie, urologists, medical and clinical/radiation oncologists, radi-

Table 4 – Summary of systematic review findings: most common reclassification definitions during DAT.

Gleason score	Clinical T category	PSA doubling time	No. of positive cores	Core involvement (%)	Patient preference	No. of studies
GSS >6	NR	NR	>2	>50	NR	14
Increase in GSS	Change in T stage	NR	NR	NR	NR	11
GSS >6	NR	NR	>3	>50%	NR	9
GSS >6	NR	NR	>2	>20%	NR	7
GSS >6	NR	NR	NR	NR	NR	7
Increase in GSS	Change in T-stage	NR	NR	Multiple	Yes	6
GSS >6	>T2	<3	>2	NR	NR	5
GSS ≥4+3	≥T2c	<3	>3	NR	NR	4

DAT = deferred active treatment; GSS = Gleason score; NR = not recorded; PSA = prostate-specific antigen.

ologists, pathologists, and specialist nurses) and patients were purposefully sampled to participate. The list of organisations that participated is included in the Supplementary material. These organisations were targeted owing to the expertise of their membership. Organisations provided participants by either nominating individuals or cascading the invitation to their entire membership. Informed consent was assumed if participants registered and completed the survey.

In the online questionnaire, participants were presented with statements and asked to rate their strength of agreement on a scale of 1 (strongly disagree) to 9 (strongly agree). Participants could also suggest additional statements for incorporation into the following round. In round 2, participants were provided with information regarding their own score from round 1 as well as a summary of the scores for the entire cohort, and could either revise or retain their original scores. Thresholds regarding what constituted "consensus agreement" and "consensus disagreement" were specified a priori [8]. "Consensus agreement" was defined as ≥70% of participants scoring a statement as "strongly agree" (7–9) and <15% of participants scoring as "strongly disagree" (1–3). Conversely, "consensus disagreement" was defined as statements scored as "strongly disagree" (score 1–3) by ≥70% of participants and "strongly agree" by <15% of participants (7–9). All other statements not falling in the above categories will be classified as equivocal. The decision to use 70% as a threshold was based on prior studies and consensus method research [10–13].

Phase 3 consisted of a 1-d face-to-face consensus group meeting attended by representatives from all stakeholder groups, and chaired by a nonvoting clinician and nonvoting methodologist. Participants were sampled from those who completed both rounds of the Delphi survey. All participants were provided with a personalised printout containing a reminder of how they scored each statement in both rounds of the Delphi, and were given the summary of group results for all statements. All statements not achieving consensus in phase 2 were discussed, reviewed, and voted upon by participants, using the same consensus thresholds from phase 2, using live voting software [8]. At the end of phase 3, a final list of consensus statements organised according to the domains of DAT were ratified by the consensus group participants and project steering group.

3. Results

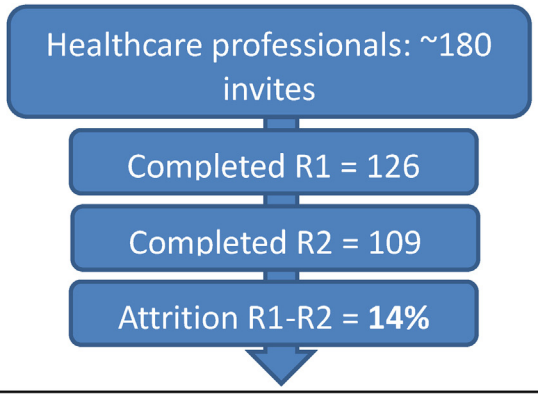
3.1. Delphi survey

Round 1 of the Delphi survey was generated from the systematic review findings (Supplementary material). A total of 127 statements were organised under the following domains and subdomains: (1) patient eligibility, inclusion, and exclusion criteria: (a) age and life expectancy, (b) risk classification (including D'Amico or EAU risk groups, prostate-specific antigen [PSA] elements, Gleason sum score/International Society of Urological Pathology grade group, clinical stage, etc.), (c) histopathological characteristics (including how biopsy is performed, extent of disease, etc.), and (d) imaging characteristics (including issues regarding multiparametric magnetic resonance imaging [mpMRI], etc.); (2) monitoring and follow-up criteria (including issues regarding frequency and nature of PSA testing, repeat biopsy, clinical examination by digital rectal examination, and imaging); (3) reclassification and change in management criteria and triggers: (a) patient characteristics, (b) PSA kinetics, (c) histopathology (including change in grade or disease extent), (d) clinical examination, (e) imaging, and (f) patient preference; and (4) outcome measures that must be prioritised in DAT programmes (including oncological, functional, and quality of life outcomes).

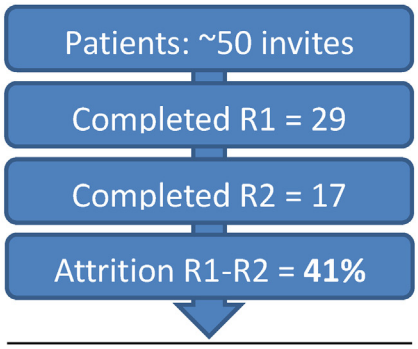
A total of 180 HCPs involved with DAT were identified through international specialist societies (Supplementary material) and invited to participate. Fifty patients identified through patient advocacy organisations (Supplementary material) were invited to complete the patient-relevant parts of the survey (ie, outcome measures that should be prioritised). Two additional statements suggested by the participants were added to the questionnaire in round 2 (Supplementary material), bringing the total number of statements to 129. In total, 126 HCPs (70% of those invited) and 29 patients (58% of those invited) completed round 1, and 109 HCPs (61% of those invited) and 17 patients (34% of those invited) completed both rounds of the survey. The attrition rates between rounds 1 and 2 were 14% for HCPs and 41% for patients. The supplementary material outlines the list of Delphi participants organised by the stakeholder group (ie, HCPs or patients), including details such as name, speciality, and country of residence for HCPs, and previous treatment, age, and country of residence for patients.

Table 5 summarises the characteristics of all Delphi participants completing both rounds of the survey, based on stakeholder groups, speciality (or relevant treatment for patients), age (for patients only), and country of residence. Table 6 summarises the survey results for all statements, organised according to consensus status (ie, consensus, near consensus, divergent opinions, or equivocal/unclear). In summary, there was consensus on 66 statements (51%) from the Delphi survey. The remaining 63 statements were brought forward for review, discussion, and voting in phase 3, to see if consensus could be achieved on them.

Table 5 – Summary of characteristics of Delphi participants completing round 1 (R1) and round 2 (R2).



Speciality	R1, *n* (%)	R2, *n* (%)
Clinical or radiation oncology	14 (11)	12 (11)
Medical oncology	3 (2)	2 (2)
Other	3 (2)	3 (3)
Pathology	7 (6)	7 (6)
Specialist nurse	8 (6)	7 (6)
Urology	82 (65)	70 (64)
Radiology	9 (7)	8 (7)
Total	126	109



Nationality	R1, *n*	R2, *n*
UK	14	10
Germany	1	0
The Netherlands	3	1
Belgium	5	3
Ireland	1	0
Portugal	1	1
Sweden	1	1
Switzerland	1	1
Slovakia	1	0
Cyprus	1	0
Total	29	17

3.2. *Consensus group meeting*

The consensus group meeting was held in Amsterdam, The Netherlands on November 9, 2018 during the 10th European Multidisciplinary Congress on Urological Cancers (ie, EMUC 2018). The meeting was attended by 35 voting participants (32 HCPs and three patients) and chaired by a nonvoting clinician and a nonvoting methodologist. Table 7 summarises the characteristics of consensus meeting participants based on stakeholder group, speciality, and country of residence. Table 8 summarises the results for all statements reviewed, discussed, and voted upon, organised according to consensus status "yes/no" (ie, in summary, 27/63 statements [43%] achieved consensus during the meeting).

3.3. *Final consensus statements and recommendations from the DETECTIVE study*

Table 9 summarises all the consensus statements obtained from all phases of the study. In total, 93 statements out of a total 129 (72%) achieved full consensus. The majority of these were achieved from the Delphi survey (71%), whilst the consensus group meeting contributed 29% to the consensus statements. Of the consensus statements, 53% were "consensus agree", whilst 48% were "consensus disagree". Consensus was achieved in at least 65% of statements across all domains across the Delphi and consensus meeting process. Table 10 lists all clinical practice recommendations based on the consensus statements.

4. Discussion

4.1. *Principal findings*

This project explored and defined key areas of controversy and uncertainty covering all the main domains of DAT, a large undertaking not previously attempted on this scale using transparent methodology. A mixed method approach was used to investigate this pressing problem, incorporating a systematic review, a two-round Delphi survey, and a face-to-face consensus meeting with international participation from key stakeholders. The systematic review confirmed the scale and scope of the problem, highlighting significant heterogeneity, inconsistency, and variability in clinical practice across all domains in contemporary studies of DAT. Given such heterogeneity, it is not surprising to note that currently, there are no conclusive data on how different DAT

Table 6 – Summary of statements and consensus status after two rounds of Delphi survey.[a,b]

		Health care professionals (HCPs)						Patients				
Domain	Item number in Delphi and description	HCPs % disagree (1–3)	HCPs % equivocal (4–6)	HCPs % agree (7–9)	HCPs total *N*	HCPs unable to score *N*	Consensus	Patients % disagree (1–3)	Patients % equivocal (4–6)	Patients % agree (7–9)	Patients total *N*	Patients unable to score *N*
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	1. There is no lower or upper age limit for inclusion as long as the appropriate life expectancy criterion is fulfilled	3.7	0.9	95.4	109	0	1	NA	NA	NA	NA	NA
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	2. The appropriate life expectancy criterion for inclusion is: (i) ≥10 yr	1.8	4.6	93.6	109	0	1	NA	NA	NA	NA	NA
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	3. The appropriate life expectancy criterion for inclusion is: (ii) ≥15 yr	18.5	45.4	36.1	109	1	4	NA	NA	NA	NA	NA
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	4. Life expectancy in everyday practice is best evaluated by: (i) performance status (eg, ECOG, Karnofsky)	8.8	46.1	45.1	109	7	4	NA	NA	NA	NA	NA
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	5. Life expectancy in everyday practice is best evaluated by: (ii) comorbidity index measure (eg, Charlson)	5.1	38.4	56.6	109	10	3	NA	NA	NA	NA	NA
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	6. Life expectancy in everyday practice is best evaluated by: (iii) Health status screening (eg, Geriatric 8 screening tool)	6.5	45.2	48.4	109	16	4	NA	NA	NA	NA	NA
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	7. Life expectancy in everyday practice is best evaluated by: (iv) combination of performance status, comorbidity index, and health status screening	0.0	4.9	95.1	109	7	1	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	8. Low-risk disease: (i) is an automatic inclusion criterion regardless of other disease factors	50.0	8.3	41.7	108	0	3	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	9. Low-risk disease: (ii) is excluded if the extent of disease is high, based on biopsy core volume, length, or number or proportion of core positivity	28.7	8.3	63.0	108	0	3	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	10. Low-risk disease: (iii) is excluded if the extent and/or stage of disease is high based on mpMRI	14.8	21.3	63.9	108	0	2	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	11. Low-risk disease: (iv) is excluded if mpMRI suggests biologically aggressive disease	17.8	21.5	60.7	108	1	2	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	12. Gleason 3 + 4 = 7 (ISUP grade 2): (i) is an automatic exclusion criterion	69.4	18.5	12.0	108	0	2	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	13. Gleason 3 + 4 = 7 (ISUP grade 2): (ii) can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a), and biopsy characteristics (low core positivity)	7.4	15.7	76.9	108	0	1	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	14. Gleason 4 + 3 = 7 (ISUP grade 3): (i) is an automatic exclusion criterion	5.6	7.4	87.0	108	0	1	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	15. Gleason 4 + 3 = 7 (ISUP grade 3): (ii) can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a), and biopsy characteristics (low core positivity)	72.2	12.0	15.7	108	0	2	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	16. PSA: (i) >10 ng/ml is an automatic exclusion criterion, regardless of other disease characteristics	78.7	13.9	7.4	108	0	1	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	17. PSA: (ii) >20 ng/ml is an automatic exclusion criterion, regardless of other disease characteristics	19.4	12.0	68.5	108	0	2	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	18. PSA density: (i) is an important inclusion criterion	18.1	22.9	59.0	108	3	3	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	19. PSA density: (ii) for inclusion should be ≤0.15 ng/ml/g	16.3	32.7	51.0	108	4	3	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	20. PSA density: (iii) for inclusion should be ≤0.20 ng/ml/g	32.4	56.9	10.8	108	6	4	NA	NA	NA	NA	NA
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	21. Clinical stage: (i) ≥T2b is an automatic exclusion criterion, regardless of other disease characteristics	38.0	36.1	25.9	108	0	4	NA	NA	NA	NA	NA

2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	22. Clinical stage: (ii) ≥T2c is an automatic exclusion criterion, regardless of other disease characteristics	17.6	8.3	74.1	108	0	2	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	23. Targeted biopsies should be reported separately from systematic biopsies	0.0	0.0	100.0	108	0	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	24. The extent of disease should be reported in: (i) length (mm)	0.9	2.8	96.3	108	0	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	25. The extent of disease should be reported in (ii) % tumour volume (as a proportion of total volume of core)	5.6	7.4	87.0	108	0	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	26. ISUP grade (Gleason score) should be reported for each positive core	4.7	1.9	93.5	108	1	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	27. Percentage of Gleason pattern 4 carcinoma should be provided for each biopsy site with Gleason score 7 carcinoma	1.9	1.9	96.3	108	1	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	28. Intraductal and cribriform histology are exclusion criteria	1.0	10.5	88.6	108	3	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	29. When systematic biopsies are performed, the extent of disease based on histological characteristics (eg, core length, core volume, core positivity, etc.) is an important inclusion/exclusion criterion	2.8	6.5	90.7	108	0	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	30. Extent of disease on histology is important even for Gleason 3 + 3 = 6/ISUP grade 1 disease because it may lead to patients being excluded	14.2	9.4	76.4	108	2	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	31. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (i) core positivity >20%	89.3	7.8	2.9	108	5	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	32. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (ii) core positivity >33%	71.8	23.3	4.9	108	5	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	33. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (iii) core positivity ≥50%	58.3	11.7	30.1	108	5	3	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	34. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (iv) positive cores >2	81.6	10.7	7.8	108	5	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	35. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (v) positive cores >3	73.8	11.7	14.6	108	5	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	36. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (vi) core length >3 mm	93.1	3.9	2.9	108	6	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	37. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (vii) core length >5 mm	87.3	7.8	4.9	108	6	1	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	38. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (i) core positivity >20%	52.0	24.5	23.5	108	6	3	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	39. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (ii) core positivity >33%	42.7	30.1	27.2	108	5	4	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	40. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease	26.2	8.7	65.0	108	5	3	NA	NA	NA	NA	NA

	characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (iii) core positivity ≥50%											
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	41. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3+4=7/ISUP Grade 2 disease is: iv. Positive cores >2	25.2	24.3	50.5	108	5	3	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	42. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (v) positive cores >3	29.1	15.5	55.3	108	5	3	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	43. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (vi) core length >3 mm	51.5	23.3	25.2	108	5	3	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	44. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (vii) core length >5 mm	36.9	28.2	35.0	108	5	4	NA	NA	NA	NA	NA
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	45. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (viii) any disease extent (because Gleason 3 + 4 = 7/ISUP grade 2 is an automatic exclusion)	78.6	8.7	12.6	108	5	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	46. If a patient has had upfront mpMRI followed by systematic and targeted biopsies, there is no need for confirmatory biopsies	17.8	7.5	74.8	108	1	2	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	47. If targeted biopsies based upon mpMRI images are performed, the number of positive cores is not an indicator of extent of disease or tumour volume	5.7	22.6	71.7	108	2	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	48. The number of positive sextants based on systematic and/or targeted biopsies should be taken into account as an indicator of tumour volume	0.9	11.1	88.0	108	0	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	49. The volume of the dominant lesion seen on mpMRI (PI-RADS V2 ≥3) should be taken into account as an indicator of tumour volume	2.8	12.1	85.0	108	1	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	50. For inclusion, prostate biopsies should be performed by: (i) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) without systematic biopsies	86.9	9.3	3.7	108	1	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	51. For inclusion, prostate biopsies should be performed by: (ii) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies	2.8	3.7	93.5	108	1	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	52. For inclusion, prostate biopsies should be performed by: (iii) transperineal template biopsies instead of mpMRI-guided biopsies	71.0	23.4	5.6	108	1	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	53. For inclusion, prostate biopsies should be performed by: (iv) TRUS-guided systematic biopsies only	79.4	15.9	4.7	108	1	1	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	54. Tumour volume (for ≤T2 disease) based purely on mpMRI characteristics is an important inclusion/exclusion criterion	32.4	25.0	42.6	108	0	4	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	55. Disease aggressiveness (for ≤T2 disease; eg, low ADC value) based purely on mpMRI characteristics is an important inclusion/exclusion criterion	51.9	33.0	15.1	108	2	3	NA	NA	NA	NA	NA
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	56. For inclusion, all patients need mpMRI at some point	11.1	5.6	83.3	108	0	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	57. During active surveillance in the first 2 yr, men should: (i) have their PSA checked every 3 mo	37.4	20.6	42.1	108	1	4	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	58. During active surveillance in the first 2 yr, men should: (ii) have their PSA checked every 6 mo	13.1	6.5	80.4	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	59. During active surveillance in the first 2 yr, men should: (iii) have not checked their PSA at all	100.0	0.0	0.0	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	60. During active surveillance after the first 2 yr, men should: (i) have their PSA checked every 3 mo	86.0	8.4	5.6	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	61. During active surveillance after the first 2 yr, men should: (ii) have their PSA checked every 6 mo	2.8	4.7	92.5	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	62. During active surveillance after the first 2 yr, men should: (iii) not have their PSA at all	100.0	0.0	0.0	108	1	1	NA	NA	NA	NA	NA

5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	63. During active surveillance, men should have a digital rectal examination (DRE)	9.3	6.5	84.1	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	64. During active surveillance, men should have a DRE: (i) every 3 mo	94.4	5.6	0.0	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	65. During active surveillance, men should have a DRE: (ii) every 6 mo	61.7	12.1	26.2	108	1	3	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	66. During active surveillance, men should have a DRE: (iii) every 12 mo	16.8	14.0	69.2	108	1	2	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	67. During active surveillance, men: need: not have a DRE	84.1	7.5	8.4	108	1	1					
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	68. During active surveillance, repeat biopsy should: (i) be performed every 12 mo	79.4	9.3	11.2	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	69. During active surveillance, repeat biopsy should: (ii) be performed every 24 mo	55.1	17.8	27.1	108	1	3	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	70. During active surveillance, repeat biopsy should: (iii) be performed every 48 mo	77.6	15.0	7.5	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	71. During active surveillance, repeat biopsy should: (iv) be performed: (iv) at 1, 4, and 7 yr	20.8	26.4	52.8	108	2	3	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	72. During active surveillance, repeat biopsy should: (v) not be preplanned routinely unless triggered	62.6	9.3	28.0	108	1	3	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	73. During active surveillance, repeat biopsy should be performed: (vi) triggered by a change in mpMRI (ie, increase PI-RADS score, lesion volume or radiological T stage)	2.8	3.7	93.5	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	74. During active surveillance, repeat biopsy should be performed: (vii) triggered by PSA doubling time <3 yr	13.2	17.9	68.9	108	2	2	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	75. During active surveillance, repeat biopsy should be performed: (viii) triggered by DRE progression	9.3	6.5	84.1	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	76. If repeat biopsies are needed, they should be performed by: (i) 10–12-core TRUS guided	44.3	18.9	36.8	108	2	4	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	77. If repeat biopsies are needed, they should be performed by: (ii) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) without systematic biopsies	70.1	13.1	16.8	108	1	2	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	78. If repeat biopsies are needed, they should be performed by: (iii) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies	3.7	2.8	93.5	108	1	1	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	79. If repeat biopsies are needed, they should be performed by: (iv) transperineal template biopsies instead of mpMRI-guided biopsies	69.8	23.6	6.6	108	2	2	NA	NA	NA	NA	NA
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	80. If repeat biopsies are needed, they should be performed by: (v) TRUS-guided systematic biopsies	57.0	19.6	23.4	108	1	3	NA	NA	NA	NA	NA
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	81. Reclassification should apply only to patients with life expectancy of ≥10 yr at the time of assessment	7.6	7.6	84.8	108	3	1	NA	NA	NA	NA	NA
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	82. Reclassification should apply only to patients with life expectancy of ≥15 yr at the time of assessment	34.3	39.0	26.7	108	3	4	NA	NA	NA	NA	NA
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	83. Active surveillance should be continued only in patients with life expectancy of ≥10 yr	9.5	1.9	88.6	108	3	1	NA	NA	NA	NA	NA
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	84. Active surveillance should be continued only in patients with life expectancy of ≥15 yr	38.1	33.3	28.6	108	3	4	NA	NA	NA	NA	NA
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	85. Patient anxiety or depression is a valid reason for triggering reclassification (including active treatment)	6.5	9.3	84.1	108	1	1	NA	NA	NA	NA	NA
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	86. Patient reluctance to undergo repeat biopsies or repeat imaging is a valid reason for triggering reclassification (including active treatment)	17.8	18.7	63.6	108	1	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	87. PSA progression is sufficient to indicate reclassification in the absence of other factors	72.2	8.3	19.4	108	0	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	88. A rise in PSA mandates rebiopsy irrespective of other findings	66.7	14.8	18.5	108	0	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	89. A rise in PSA mandates reimaging of the patient	19.4	14.8	65.7	108	0	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance	90. Shortening of PSA doubling time: (i) is sufficient to indicate reclassification in	68.2	16.8	15.0	108	1	2	NA	NA	NA	NA	NA

for an active treatment) criteria. 2. Based on PSA	the absence of other factors											
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	91. Shortening of PSA doubling time: (ii) should indicate reclassification only if it falls below a defined threshold	39.6	25.5	34.9	108	2	4	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	92. Shortening of PSA doubling time: (iii) of <36 mo indicates reclassification	65.7	30.5	3.8	108	3	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	93. Shortening of PSA doubling time: (iv) of <24 mo indicates reclassification	47.6	23.8	28.6	108	3	4	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	94. Shortening of PSA doubling time: (v) even if minimal, would indicate reclassification if accompanied by other PSA-based parameter changes	62.3	30.2	7.5	108	2	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	95. A rise in PSA above an absolute threshold: (i) of >10 would indicate reclassification	67.0	14.2	18.9	108	2	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	96. A rise in PSA above an absolute threshold: (ii) of >20 would indicate reclassification	24.5	11.3	64.2	108	2	3	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	97. A PSA velocity: (i) of >0.75/yr would indicate reclassification	62.7	36.3	1.0	108	6	2	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	98. A PSA velocity: (ii) of >1.0/yr would indicate reclassification	52.9	37.3	9.8	108	6	3	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	99. An increase in PSA density: (i) is sufficient to indicate reclassification in the absence of other factors	70.5	27.6	1.9	108	3	1	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	100. An increase in PSA density: (ii) would indicate reclassification if accompanied by other PSA-based parameter changes	42.9	48.6	8.6	108	3	4	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	101. A change in PSA parameters, which by itself is not sufficient, would indicate reclassification if accompanied by: (i) changes in histology	0.9	0.0	99.1	108	1	1	NA	NA	NA	NA	NA
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	102. A change in PSA parameters, which by itself is not sufficient, would indicate reclassification if accompanied by: (ii) changes in imaging	10.3	20.6	69.2	108	1	2	NA	NA	NA	NA	NA
8. Reclassification (ie, leaving active surveillance for an active treatment)	103. A higher Gleason score (or ISUP grade) on rebiopsy is required for reclassification	15.9	3.7	80.4	108	1	2	NA	NA	NA	NA	NA
criteria. 3. Based on histopathology grade												
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	104. An increase in the number of positive cores on rebiopsy: (i) indicates reclassification (ie, no threshold needed)	65.7	19.4	14.8	108	0	2	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	105. An increase in the number of positive cores on rebiopsy: (ii) if >2 cores on rebiopsy indicates reclassification	58.3	29.6	12.0	108	0	3	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	106. An increase in the number of positive cores on rebiopsy: (iii) if >3 cores on rebiopsy indicates reclassification	40.7	21.3	38.0	108	0	4	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	107. An increase in the extent of core involvement: (i) indicates reclassification (ie, no threshold needed)	74.1	19.4	6.5	108	0	1	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	108. An increase in the extent of core involvement: (ii) if >20% of a core indicates reclassification	73.1	24.1	2.8	108	0	1	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	109. An increase in the extent of core involvement: (iii) if >33% of a core indicates reclassification	57.4	30.6	12.0	108	0	3	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	110. An increase in the extent of core involvement: (iv) if >50% of a core indicates reclassification	32.4	28.7	38.9	108	0	4	NA	NA	NA	NA	NA
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	111. An increase in the extent of core involvement: (v) is not important for Gleason 3 + 3 = 6/ISUP grade 1 disease	33.3	17.6	49.1	108	0	4	NA	NA	NA	NA	NA
10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	112. An increase in the clinical T category based on DRE, as the sole criterion: (i) if increase to cT2aindicates reclassification	78.5	15.9	5.6	108	1	1	NA	NA	NA	NA	NA
10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	113 An increase in the clinical T category based on DRE, as the sole criterion: (ii) if increase to cT2b indicates reclassification	56.1	21.5	22.4	108	1	3	NA	NA	NA	NA	NA

10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	114. An increase in the clinical T category based on DRE, as the sole criterion: (iii) if increase to cT2c indicates reclassification	31.8	5.6	62.6	108	1	3	NA	NA	NA	NA	NA
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	115. Radiological evidence of disease progression is sufficient to reclassify in the absence of other factors	62.6	15.0	22.4	108	1	3	NA	NA	NA	NA	NA
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	116. Radiological evidence of progression mandates an image-directed biopsy	0.9	4.7	94.4	108	1	1	NA	NA	NA	NA	NA
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	117. A new focus of cancer on repeat imaging indicates reclassification: (i) always	75.7	19.6	4.7	108	1	1	NA	NA	NA	NA	NA
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	118. A new focus of cancer on repeat imaging indicates reclassification: (ii) only if accompanied by a rebiopsy	0.9	4.7	94.4	108	1	1	NA	NA	NA	NA	NA
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	119. Increase in tumour volume (for ≤T2 disease) on imaging alone (ie, in the absence of rebiopsy, PSA, etc.) indicates reclassification	72.0	21.5	6.5	108	1	1	NA	NA	NA	NA	NA
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	120. An increase in the PI-RADS score indicates reclassification in the absence of other features	73.6	16.0	10.4	108	2	1	NA	NA	NA	NA	NA
12. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 7. Based on patient preference	121. Patient preference to switch to active treatment, regardless of other factors, should trigger reclassification	5.6	8.4	86.0	108	1	1	NA	NA	NA	NA	NA
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	122. Overall survival (ie, how long you live, between your diagnosis and dying from any cause) is a critically important outcome for clinicians to measure for men on active surveillance	2.8	0.9	96.3	108	0	1	6%	19%	75%	16	0
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	123. Prostate cancer–specific survival (ie, how long you live, between your diagnosis and dying from prostate cancer) is a critically important outcome to measure for men on active surveillance	1.9	0.0	98.1	108	0	1	6%	19%	75%	16	0
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	124. Progression to metastatic disease (ie, your cancer spreading to other organs) is a critically important outcome to measure for men on active surveillance	0.0	0.9	99.1	108	0	1	6%	0%	94%	16	0
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	125. Local progression (ie, your cancer getting bigger or more advanced locally) is a critically important outcome to measure for men on active surveillance	1.9	10.2	88.0	108	0	1	0%	0%	100%	16	0
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	126. Symptomatic progression (ie, your cancer progressing locally to cause symptoms such as pain, bleeding in urine, difficulty in urinating, etc.) is a critically important outcome to measure for men on active surveillance	0.0	1.9	98.1	108	0	1	0%	0%	100%	16	0
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	127. Reclassification (ie, switching from active surveillance to active curative treatment, eg, surgery or radiotherapy) is a critically important outcome to measure for men on active surveillance	0.0	3.7	96.3	108	0	1	0%	6%	94%	16	0
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	128. Urinary function (ie, problems relating to passing urine) is a critically important outcome to measure for men on active surveillance	2.8	11.1	86.1	108	0	1	0%	13%	87%	16	1
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	129. Sexual function (ie, problems relating to erection, libido, ejaculation, etc.) is a critically important outcome to measure for men on active surveillance	1.9	12.0	86.1	108	0	2	7%	27%	67%	16	1
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	130. Overall quality of life (ie, satisfaction with general health and well-being) is a critically important outcome to measure for men on active surveillance	0.0	0.9	99.1	108	0	1	0%	0%	100%	16	1
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	131. Anxiety (due to your cancer or treatment) is a critically important outcome to measure for men on active surveillance	0.0	1.9	98.1	108	0	1	7%	7%	87%	16	1
13. Outcome measures: primary outcome measures that must be measured and prioritised by all active surveillance programmes	132. Depression (due to your cancer or treatment) is a critically important outcome to measure for men on active surveillance	0.0	2.8	97.2	108	0	1	7%	7%	87%	16	1
Additional R2	9991. Biomarkers are useful in stratifying risk of disease progression for men undergoing active surveillance	25.0	38.5	36.5	108	4	4	NA	NA	NA	NA	NA
Additional R3	9992. Men known to carry the BRAC2 mutation are ineligible for active surveillance	30.9	30.9	38.1	108	11	4	NA	NA	NA	NA	NA

ADC = apparent diffusion coefficient; *BRAC2* = DNA repair associated gene; DRE = digital-rectal examination; ECOG = Eastern Cooperative Oncology Group (performance status); GSS = Gleason score; HCP = healthcare professional; ISUP = International Society of Urological Pathology; mpMRI = multi-parametric magnetic resonance imaging; *N* = number; NA = not applicable; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; R2 = round 2; R3 = round 3; TRUS = transrectal ultrasound.

[a] In columns showing percentages agree/equivocal/disagree, red shaded cells indicate ≥70% and yellow shaded cells indicate 60–70%.

[b] In "consensus" column:

1	Consensus (≥70% agree and ≤15% disagree, or vice versa). No further discussion required, not taken forward to face-to-face meeting.
2	Near consensus (≥70% agree but ≥15% disagree, or vice versa; or ≥60% agree, and ≤20% disagree, or vice versa). Taken forward to discuss and vote in face-to-face meeting.
3	Divergent opinions (eg, >50% agree and >25% disagree). Taken forward to discuss and vote in face-to-face meeting.
4	Equivocal or unclear results (eg, not >50% in any cell; or majority equivocal). Taken forward to discuss and vote in face-to-face meeting.

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Table 7 – Summary of characteristics of consensus meeting participants.

Name	Role	Country of residence
Erik Briers	Patient	Belgium
Christopher Wallis	Urologista	Canada
Philippe Violette	Urologist	Canada
Jacques Irani	Chair (urologist)	France
Alberto Bossi	Oncologist	France
Olivier Rouvière	Radiologist	France
Raphaele Renard-Penna	Radiologist	France
Nicolas Mottet	Urologist	France
Thomas Wiegel	Radiation oncologist	Germany
Derya Tilki	Urologist	Germany
Michael Lardas	Urologist	Greece
Nikolaos Grivas	Urologist	Greece
Maurizio Colecchia	Pathologist	Italy
Giorgio Gandaglia	Urologist	Italy
Alberto Briganti	Urologist	Italy
Maria J Ribal	Urologist	Spain
Anders Bjartell	Urologist	Sweden
Christian Fankhauser	Urologist	Switzerland
Monique Roobol	Epidemiologist	The Netherlands
Arno Van Leenders	Pathologist	The Netherlands
Ruud Baanders	Patient	The Netherlands
Ivo Schoots	Radiologist	The Netherlands
Peter-Paul Willemse	Urologist	The Netherlands
Michiel Sedelaar	Urologist	The Netherlands
Chris Bangma	Urologist	The Netherlands
Theo van der Kwast	Pathologist	The Netherlands/Canada
Jeff Davies	Patient	UK
Jonathan Richenberg	Radiologist	UK
Malcolm Mason	Radiotherapist	UK
Thomas Lam	Urologist	UK
James N'Dow	Urologist	UK
Catherine Paterson	Urology nurse consultant and research fellow	UK
Karen Wilkinson	Uro-oncology nurse specialist	UK
Steven MacLennan	Chair (methodologist)	UK
Philip Cornford	Urologist	UK
Silke Gillessen	Oncologist	UK/Switzerland
Brett Cox	Radiation oncologist	USA

strategies compare with one another and which strategy, definition, and threshold should be adopted in clinical practice and clinical trials. Although several seminal randomised controlled trials investigating the effectiveness of observation [1,2] or active monitoring [3] as a management strategy for localised prostate cancer in comparison with active curative treatment have been published, these studies do not represent current practice of DAT, which has continued to evolve over the past 15 yr, especially with the introduction of new technology such as mpMRI scan into the patient care pathway, changes in the reporting of prostate cancer grade, and more accurate ways of performing prostate biopsies (including MRI-targeted biopsies or transperineal template biopsies). There is, therefore, an urgent need to provide guidance to clinicians, patients, researchers, and policymakers, and in the absence of high levels of evidence, the only available option is to issue consensus statements using robust, transparent, and reproducible methods. Our project set out to achieve this objective, and ultimately consensus was achieved in >72% of statements covering all the domains of DAT; the results will provide the basis for international guidance and drive the research agenda for the immediate future. The main recommendations based on the consensus statements are listed in Table 10.

4.2. Relevance and impact of study findings on clinical practice and research

Our study, with participation from HCPs and patients, has provided the basis for conduct of DAT. Consensus statements represent the lowest level of evidence (ie, level 5) on the evidence-based medicine hierarchy [14], but in areas where there is low certainty and conflicting evidence, they represent a pragmatic basis for interim guidance. Consensus statements should be regarded as a starting point for clinicians and researchers to guide studies that will provide higher-quality evidence and increase certainty. Evidence is never complete; it is ever evolving, and correspondingly recommendations require updating as necessary. Using our consensus statements as a basis for informing and guiding the conduct of DAT, there is a need for clinicians to prospectively collect and audit data on DAT in routine clinical practice, and for researchers and trialists to conduct clinical trials or prospective comparative studies so that clinical effectiveness data can be obtained. In this context, initiatives such as PIONEER [15] and the Movember Foundation's Global Action Plan Active Surveillance (GAP3) project, which aims to establish a global prospective database [16], represent important initial steps.

Table 8 – Consensus meeting: summary of statements discussed, reviewed, and voted upon, and consensus status—consensus (yes/no/not voted[a]).

Domain	Item number from Delphi and description	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Consensus yes/no/not voted
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	3. The appropriate life expectancy criterion for inclusion is: (ii) ≥15 yr	0	0	0	NA	Not voted
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	4. Life expectancy in everyday practice is best evaluated by: (i) performance status (eg, ECOG, Karnofsky)	0	0	0	NA	Not voted
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	5. Life expectancy in everyday practice is best evaluated by: (ii) comorbidity index measure (eg, Charlson)	0	0	0	NA	Not voted
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	6. Life expectancy in everyday practice is best evaluated by: (iii) health status screening (eg, Geriatric 8 screening tool)	0	0	0	NA	Not voted
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	8. Low-risk disease: (i) is an automatic inclusion criterion regardless of other disease factors	0	0	0	NA	Not voted
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	9. Low-risk disease: (ii) is excluded if the extent of disease is high, based on biopsy core volume, length, or number or proportion of core positivity	46	15	39	28	No
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	10. Low-risk disease: (iii) is excluded if the extent and/or stage of disease is high based on mpMRI	7	9	84	30	Yes
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	11. Low-risk disease: (iv) is excluded if mpMRI suggests biologically aggressive disease	23	27	50	30	No
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	12. Gleason 3 + 4 = 7 (ISUP grade 2): (i) is an automatic exclusion criterion	80	6	13	29	Yes
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	15. Gleason 4 + 3 = 7 (ISUP grade 3): (ii) can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a), and biopsy characteristics (low core positivity)	97	3	0	27	Yes
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	17. PSA: (ii) >20 ng/ml is an automatic exclusion criterion, regardless of other disease characteristics	55	0	45	29	No
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	18. PSA density: (i) is an important inclusion criterion	7	15	78	28	Yes
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	19. PSA density: (ii) for inclusion should be ≤0.15 ng/ml/g	12	24	64	24	No
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	20. PSA density: (iii) for inclusion should be ≤0.20 ng/ml/g	52	32	16	25	No
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	21. Clinical stage: (i) ≥T2b is an automatic exclusion criterion, regardless of other disease characteristics	78	9	13	23	Yes
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	22. Clinical stage: (ii) ≥T2c is an automatic exclusion criterion, regardless of other disease characteristics	8	0	92	26	Yes
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	33. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (iii) core positivity ≥50%	92	4	4	23	Yes
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	38. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (i) core positivity >20%	64	18	18	28	No
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	39. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (ii) core positivity >33%	48	24	28	25	No
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	40. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (iii) core positivity ≥50%	30	33	37	27	No
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	41. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (iv) positive cores >2	34	18	48	27	No
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	42. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (v) positive cores >3	30	19	51	27	No
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	43. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (vi) core length >3 mm	64	24	12	25	No
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	44. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (vii) core length >5 mm	50	27	23	26	No
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	46. If a patient has had upfront mpMRI followed by systematic and targeted biopsies, there is no need for confirmatory biopsies	10	8	82	28	Yes
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	54. Tumour volume (for ≤T2 disease) based purely on mpMRI characteristics is an important inclusion/exclusion criterion	68	0	32	25	No
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	55. Disease aggressiveness (for ≤T2 disease; eg, low ADC value) based purely on mpMRI characteristics is an important inclusion/exclusion criterion	74	14	12	27	Yes
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	57. During active surveillance in the first 2 yr, men should have their PSA checked: (i) every 3 mo	27	10	63	29	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	65. During active surveillance, men should have a digital rectal examination (DRE): (ii) every 6 mo	79	4	17	28	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	66. During active surveillance, men should have a DRE: (iii) every 12 mo	10	17	72	29	Yes
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	69. During active surveillance, repeat biopsy should be performed: (ii) every 24 mo	73	10	17	30	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	71. During active surveillance, repeat biopsy should be performed: (iv) at 1, 4, and 7 yr	22	30	48	27	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	72. During active surveillance, repeat biopsy should be performed: (v) not routinely re-planned unless triggered	59	6	35	29	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	74. During active surveillance, repeat biopsy should be performed: (vii) triggered by PSA doubling time <3 yr	18	19	64	28	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	76. If repeat biopsies are needed, they should be performed by: (i) 10–12-core TRUS guided	0	0	0	NA	Not voted
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	77. If repeat biopsies are needed, they should be performed by: (ii) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) without systematic biopsies	81	3	16	30	No
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	79. If repeat biopsies are needed, they should be performed by: (iv) transperineal template biopsies instead of mpMRI-guided biopsies	90	10	0	29	Yes
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	80. If repeat biopsies are needed, they should be performed by: (v) TRUS-guided systematic biopsies	0	0	0	NA	Not voted
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	82. Reclassification should apply only to patients with life expectancy of ≥15 yr at the time of assessment	0	0	0	NA	Not voted

6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	84. Active surveillance should be continued only in patients with life expectancy of ≥15 yr	0	0	0	NA	Not voted
6. Reclassification (ie leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	86. Patient reluctance to undergo repeat biopsies or repeat imaging is a valid reason for triggering reclassification (including active treatment)	11	11	78	28	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	87. PSA progression is sufficient to indicate reclassification in the absence of other factors	84	3	13	31	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	88. A rise in PSA mandates rebiopsy irrespective of other findings.	89	0	11%	28	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	89. A rise in PSA mandates reimaging of the patient.	47	11	42	28	No
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	90. Shortening of PSA doubling time: (i) is sufficient to indicate reclassification in the absence of other factors	86	6	8	29	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	91. Shortening of PSA doubling time: (ii) should indicate reclassification only if it falls below a defined threshold	38	16	46	26	No
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	92. Shortening of PSA doubling time: (iii) of <36 mo indicates reclassification	92	4	4	28	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	93. Shortening of PSA doubling time: (iv) of <24 mo indicates reclassification	0	0	0	NA	Not voted
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	94. Shortening of PSA doubling time: (v) even if minimal would indicate reclassification if accompanied by other PSA-based parameter changes	96	4	0	25	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	95. A rise in PSA above an absolute threshold: (i) of >10 would indicate reclassification	86	7	7	29	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	96. A rise in PSA above an absolute threshold: (ii) of >20 would indicate reclassification	34	11	55	27	Not voted
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	97. A PSA velocity: (i) of >0.75/yr would indicate reclassification	92	4	4	25	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	98. A PSA velocity: (ii) of >1.0/yr would indicate reclassification	93	6	0	27	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	100. An increase in PSA density: (ii) would indicate reclassification if accompanied by other PSA-based parameter changes	82	11	7	28	Yes
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	102. A change in PSA parameters, which by itself is not sufficient, would indicate reclassification if accompanied by: (ii) changes in imaging	48	18	34	27	No
8. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 3. Based on histopathology grade	103. A higher Gleason score (or ISUP grade) on rebiopsy is required for reclassification	27	10	63	30	No
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	104. An increase in the number of positive cores on rebiopsy: (i) indicates reclassification (ie, no threshold needed)	89	0	11	27	Yes
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	105. An increase in the number of positive cores on rebiopsy: (ii) if >2 cores on rebiopsy indicates reclassification	77	4	19	26	No
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	106. An increase in the number of positive cores on rebiopsy: (iii) if >3 cores on rebiopsy indicates reclassification	64	12	24	25	No
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	109. An increase in the extent of core involvement: (iii) if >33% of a core indicates reclassification	86	4	10	27	Yes
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	110. An increase in the extent of core involvement: (iv) if >50% of a core indicates reclassification	84	8	8	25	Yes
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	111. An increase in the extent of core involvement: (v) is not important for Gleason 3 + 3 = 6/ISUP grade 1 disease	20	8	72	25	No
10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	113. An increase in the clinical T category based on DRE, as the sole criterion: (ii) if increase to cT2b indicates reclassification	88	4	8	27	Yes
10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	114. An increase in the clinical T category based on DRE, as the sole criterion: (iii) if increase to cT2c indicates reclassification	42	26	32	24	No
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	115. Radiological evidence of disease progression is sufficient to reclassify in the absence of other factors	92	0	8	26	Yes
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	129. Sexual function (ie, problems relating to erection, libido, ejaculation, etc.) is a critically important outcome to measure for men on active surveillance	3	7	90	30	Yes
Additional R2	9991. Biomarkers are useful in stratifying risk of disease progression for men undergoing active surveillance	41	28	31	22	No
Additional R3	9992. Men known to carry the BRAC2 mutation are ineligible for active surveillance	63	21	16	19	No

ADC = apparent diffusion coefficient; *BRAC2* = DNA repair associated gene; DRE = digital-rectal examination; ECOG = Eastern Cooperative Oncology Group (performance status); ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; *N* = number; NA = not applicable; PSA = prostate-specific antigen; R2 = round 2; R3 = round 3; TRUS = transrectal ultrasound.

[a] Some items were discussed by the consensus meeting group, and were decided to have been superseded by the answer to a previous question and therefore not requiring a vote.

Our results may be juxtaposed with those of other studies with overlapping aims. Bruinsma et al [7] used consensus methods to develop statements for active surveillance primarily aimed at standardising terms and definitions. The authors published a list of 61 items as a glossary of terms and definitions, whereas our study provides practical guidance for programmes of DAT. Both studies are complementary. MacLennan et al [12] used

Table 9 – Final consensus statements from the DETECTIVE study.

Domain	Item number in Delphi and description	Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	1. There is no lower or upper age limit for inclusion as long as the appropriate life expectancy criterion is fulfilled	Delphi	Agree
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	2. The appropriate life expectancy criterion for inclusion is: (i) ≥10 yr	Delphi	Agree
1. Patient eligibility, inclusion, and exclusion criteria. 1. Age and life expectancy	7. Life expectancy in everyday practice is best evaluated by: (iv) combination of performance status, comorbidity index, and health status screening	Delphi	Agree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	10. Low-risk disease: (iii) is excluded if the extent and/or stage of disease is high based on mpMRI	Meeting	Agree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	12. Gleason 3 + 4 = 7 (ISUP grade 2): (i) is an automatic exclusion criterion	Meeting	Disagree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	13. Gleason 3 + 4 = 7 (ISUP grade 2): (ii) can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a), and biopsy characteristics (low core positivity)	Delphi	Agree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	14. Gleason 4 + 3 = 7 (ISUP grade 3): (i) is an automatic exclusion criterion	Delphi	Agree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	15. Gleason 4 + 3 = 7 (ISUP grade 3): (ii) can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a), and biopsy characteristics (low core positivity)	Meeting	Disagree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	16. PSA: (i) >10 ng/ml is an automatic exclusion criterion, regardless of other disease characteristics	Delphi	Disagree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	18. PSA density: (i) is an important inclusion criterion	Meeting	Agree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	21. Clinical stage: (i) ≥T2b is an automatic exclusion criterion, regardless of other disease characteristics	Meeting	Disagree
2. Patient eligibility, inclusion, and exclusion criteria. 2. Risk classification	22. Clinical stage: (ii) ≥T2c is an automatic exclusion criterion, regardless of other disease characteristics	Meeting	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	23. Targeted biopsies should be reported separately from systematic biopsies	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	24. The extent of disease should be reported in: (i) length (mm)	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	25. The extent of disease should be reported in: (ii) % tumour volume (as a proportion of total volume of core)	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	26. ISUP grade (Gleason score) should be reported for each positive core	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	27. Percentage of Gleason pattern 4 carcinoma should be provided for each biopsy site with Gleason score 7 carcinoma	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	28. Intraductal and cribriform histologies are exclusion criteria	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	29. When systematic biopsies are performed, the extent of disease based on histological characteristics (eg, core length, core volume, core positivity, etc.) is an important inclusion/exclusion criterion	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	30. Extent of disease on histology is important even for Gleason 3 + 3 = 6/ISUP grade 1 disease because it may lead to patients being excluded	Delphi	Agree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	31. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (i) core positivity >20%	Delphi	Disagree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	32. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (ii) core positivity >33%	Delphi	Disagree

Table 9 (*Continued*)

Domain	Item number in Delphi and description	Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	33. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (iii) core positivity ≥50%	Meeting	Disagree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	34. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (iv) positive cores >2	Delphi	Disagree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	35. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (v) positive cores >3	Delphi	Disagree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	36. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (vi) core length >3 mm	Delphi	Disagree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	37. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 3 = 6/ISUP grade 1 disease is: (vii) core length >5 mm	Delphi	Disagree
3. Patient eligibility, inclusion, and exclusion criteria. 3. Pathology characteristics	45. The threshold of disease extent beyond which patients are automatically excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3 + 4 = 7/ISUP grade 2 disease is: (viii) any disease extent (because Gleason 3 + 4 = 7/ISUP grade 2 is an automatic exclusion)	Delphi	Disagree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	46. If a patient has had upfront mpMRI followed by systematic and targeted biopsies, there is no need for confirmatory biopsies	Meeting	Agree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	47. If targeted biopsies based upon mpMRI images are performed, the number of positive cores is not an indicator of the extent of disease or tumour volume	Delphi	Agree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	48. The number of positive sextants based on systematic and/or targeted biopsies should be taken into account as an indicator of tumour volume	Delphi	Agree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	49. The volume of the dominant lesion seen on mpMRI (PI-RADS V2 ≥ 3) should be taken into account as an indicator of tumour volume	Delphi	Agree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	50. For inclusion, prostate biopsies should be performed by: (i) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) without systematic biopsies	Delphi	Disagree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	51. For inclusion, prostate biopsies should be performed by: (ii) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies	Delphi	Agree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	52. For inclusion, prostate biopsies should be performed by: (iii) transperineal template biopsies instead of mpMRI-guided biopsies	Delphi	Disagree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	53. For inclusion, prostate biopsies should be performed by: (iv) TRUS-guided systematic biopsies only	Delphi	Disagree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	55. Disease aggressiveness (for ≤ T2 disease; eg, low ADC value) based purely on mpMRI characteristics is an important inclusion/exclusion criterion	Meeting	Disagree
4. Patient eligibility, inclusion, and exclusion criteria. 4. Imaging characteristics	56. For inclusion, all patients need mpMRI at some point	Delphi	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	58. During active surveillance in the first 2 yr, men should: (ii) have their PSA checked every 6 mo	Delphi	Agree

Table 9 (*Continued*)

Domain	Item number in Delphi and description	Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	59. During active surveillance in the first 2 yr, men should: (iii) not have their PSA checked at all	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	60. During active surveillance after the first 2 yr, men should: (i) have their PSA checked every 3 mo	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	61. During active surveillance after the first 2 yr, men should: (ii) have their PSA checked every 6 mo	Delphi	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	62. During active surveillance after the first 2 yr, men should: (iii) not have their PSA checked at all	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	63. During active surveillance, men should have a digital rectal examination (DRE)	Delphi	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	64. During active surveillance, men should have a DRE: (i) every 3 mo	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	66. During active surveillance, men should have a DRE: (iii) every 12 mo	Meeting	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	67. During active surveillance, men: (iv) need not have a DRE	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	68. During active surveillance, repeat biopsy should be performed: (i) every 12 mo	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	70. During active surveillance, repeat biopsy should be performed: (iii) every 48 mo	Delphi	Disagree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	73. During active surveillance, repeat biopsy should be performed: (vi) triggered by a change in mpMRI (ie, increase PI-RADS score, lesion volume, or radiological T stage)	Delphi	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	75. During active surveillance, repeat biopsy should be performed: (viii) triggered by DRE progression	Delphi	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	78. If repeat biopsies are needed, they should be performed by: (iii) mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies	Delphi	Agree
5. Monitoring and follow-up criteria. 1. Monitoring and follow-up	79. If repeat biopsies are needed, they should be performed by: (iv) transperineal template biopsies instead of mpMRI-guided biopsies	Meeting	Disagree
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	81. Reclassification should apply only to patients with life expectancy of $\geq$10 yr at the time of assessment	Delphi	Agree
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	83. Active surveillance should be continued only in patients with life expectancy of $\geq$10 yr	Delphi	Agree
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	85. Patient anxiety or depression is a valid reason for triggering reclassification (including active treatment)	Delphi	Agree
6. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 1. Based on patient characteristics	86. Patient reluctance to undergo repeat biopsies or repeat imaging is a valid reason for triggering reclassification (including active treatment)	Meeting	Agree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	87. PSA progression is sufficient to indicate reclassification in the absence of other factors	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	88. A rise in PSA mandates rebiopsy irrespective of other findings	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	90. Shortening of PSA doubling time: (i) is sufficient to indicate reclassification in the absence of other factors	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	92. Shortening of PSA doubling time: (iii) of <36 mo indicates reclassification	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	94. Shortening of PSA doubling time: (v) even if minimal would indicate reclassification if accompanied by other PSA-based parameter changes	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	95. A rise in PSA above an absolute threshold: (i) of >10 would indicate reclassification	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	97. A PSA velocity: (i) of >0.75/yr would indicate reclassification	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	98. A PSA velocity: (ii) of >1.0/yr would indicate reclassification	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	99. An increase in PSA density: (i) is sufficient to indicate reclassification in the absence of other factors	Delphi	Disagree

Table 9 (*Continued*)

Domain	Item number in Delphi and description	Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	100. An increase in PSA density: (ii) would indicate reclassification if accompanied by other PSA-based parameter changes	Meeting	Disagree
7. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 2. Based on PSA	101. A change in PSA parameters, which by itself is not sufficient, would indicate reclassification if accompanied by: (i) changes in histology	Delphi	Agree
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	104. An increase in the number of positive cores on rebiopsy: (i) indicates reclassification (ie, no threshold needed)	Meeting	Disagree
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	107. An increase in the extent of core involvement: (i) indicates reclassification (ie, no threshold needed)	Delphi	Disagree
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	108. An increase in the extent of core involvement: (ii) if >20% of a core indicates reclassification	Delphi	Disagree
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	109. An increase in the extent of core involvement: (iii) if >33% of a core indicates reclassification	Meeting	Disagree
9. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 4. Based on histopathology extent	110. An increase in the extent of core involvement: (iv) if >50% of a core indicates reclassification	Meeting	Disagree
10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	112. An increase in the clinical T category based on DRE, as the sole criterion: (i) if increase to cT2a indicates reclassification	Delphi	Disagree
10. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 5. Based on clinical extent	113. An increase in the clinical T category based on DRE, as the sole criterion: (ii) if increase to cT2b indicates reclassification	Meeting	Disagree
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	115. Radiological evidence of disease progression is sufficient to reclassify in the absence of other factors	Meeting	Disagree
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	116. Radiological evidence of progression mandates an image-directed biopsy	Delphi	Agree
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	117. A new focus of cancer on repeat imaging indicates reclassification: (i) always	Delphi	Disagree
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	118. A new focus of cancer on repeat imaging indicates reclassification: (ii) only if accompanied by a rebiopsy	Delphi	Agree
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	119. Increase in tumour volume (for ≤T2 disease) on imaging alone (ie, in the absence of rebiopsy, PSA, etc.) indicates reclassification	Delphi	Disagree
11. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 6. Based on imaging	120. An increase in the PI-RADS score indicates reclassification in the absence of other features	Delphi	Disagree
12. Reclassification (ie, leaving active surveillance for an active treatment) criteria. 7. Based on patient preference	121. Patient preference to switch to active treatment, regardless of other factors, should trigger reclassification	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	122. Overall survival (ie, how long you live, between your diagnosis and dying from any cause) is a critically important outcome for clinicians to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	123. Prostate cancer–specific survival (ie, how long you live, between your diagnosis and dying from prostate cancer) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	124. Progression to metastatic disease (ie, your cancer spreading to other organs) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	125. Local progression (ie, your cancer getting bigger or more advanced locally) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	126. Symptomatic progression (ie, your cancer progressing locally to cause symptoms such as pain, bleeding in urine, difficulty in urinating, etc.) is a critically important outcome to measure for men on active surveillance	Delphi	Agree

Table 9 (*Continued*)

Domain	Item number in Delphi and description	Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	127. Reclassification (ie, switching from active surveillance to active curative treatment, eg, surgery or radiotherapy) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	128. Urinary function (ie, problems relating to passing urine) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	129. Sexual function (ie, problems relating to erection, libido, ejaculation, etc.) is a critically important outcome to measure for men on active surveillance	Meeting	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	130. Overall quality of life (ie, satisfaction with general health and well-being) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	131. Anxiety (due to your cancer or treatment) is a critically important outcome to measure for men on active surveillance	Delphi	Agree
13. Outcome measures. Primary outcome measures that must be measured and prioritised by all active surveillance programmes	132. Depression (due to your cancer or treatment) is a critically important outcome to measure for men on active surveillance	Delphi	Agree

ADC = apparent diffusion coefficient; DRE = digital-rectal examination; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

similar consensus methods in creating a core outcome set applicable across all interventions, including DAT. The prioritised outcome measures obtained from our study (ie, core outcomes for DAT) overlap with MacLennan et al's [12] core outcome set, providing confidence that men with localised prostate cancer and the HCPs who treat them, regarded the same outcomes as important in two separate samples. More recently, Merriel et al [17] published consensus statements on current best practice of active surveillance in the UK. The statements were developed by a multidisciplinary group of 27 members consisting of clinical experts and patient experts, informed by a review of the literature, existing guidelines and protocols used by UK urology departments, and survey data from men with localised prostate cancer. The final consensus statements were then issued by a subgroup of the panel ($n = 14$) in a face-to-face meeting. There are clear similarities between both projects, with both being informed by a review of the literature, and statements were developed by a multidisciplinary panel of clinicians and patients covering similar domains. However, there are major differences. It was unclear whether Merriel et al's [17] project was based on an a priori protocol for the systematic review (eg, Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA]) and for the consensus phases; the methods, processes and rules underpinning the consensus process, its definitions and how they were developed and achieved were not described. Our project was more international in scope, involved a larger multidisciplinary panel ($n = 125$) and was protocol-driven. We believe these are essential elements in any consensus endeavour which minimise bias, arbitrariness, and subjectivity, whilst enhancing rigour, transparency, and reproducibility. Nevertheless, there is overlap between the findings of both projects across all domains, and there are no major contradictory findings; as such both projects could be regarded as complementary.

4.3. *Strengths and limitations*

The study used robust, transparent and reproducible methods based on an *a priori* protocol. The study was international and contemporary in scope, involving patients and a large panel of HCPs purposively sampled from a broad range of disciplines, all of whom are stakeholders in DAT. A two-step, multi-phase consensus building process based on an iterative Delphi survey and consensus group meeting using anonymous voting techniques was employed, all of which enhanced internal validity. High external validity was achieved by ensuring that the survey items were informed by a systematic review of the literature, which was undertaken according to PRISMA guidelines. In terms of limitations, the project was designed to be pragmatic and practical for participants. Statements had to be brief and concise, and although participants rated their judgements on a scale, decisions were essentially binary in nature (ie, disagree or agree). Consequently, it was not possible to address all elements of uncertainty regarding DAT. In particular, the decision-making process regarding patient inclusion or exclusion or reclassification often involves a complex interplay between multiple factors and variables. The relative weighting placed on each variable as one or more variables change within and across patients, and how this affects the decision-making process for patients and clinicians are difficult to conceptualise and address meaningfully in a consensus-finding study. Secondly, within the HCPs' group, there was a higher ratio of urologists compared with other specialists, in both the Delphi survey and consensus group meeting. However, this

Table 10 – Recommendations based on consensus statements from the DETECTIVE study.

Recommendations
Eligibility, inclusion, and exclusion criteria
1. For inclusion, patients must have life expectancy of ≥10 yr, but there is no lower or upper age limit for inclusion.
2. Evaluate life expectancy using a combination of performance status, comorbidity index, and health status screening.
3. Patients with low-risk localised disease should be excluded if the extent and/or stage of disease is high based on mpMRI.
4. Patients with Gleason 3 + 4 = 7 (ISUP grade 2) should not be excluded automatically, if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a), and biopsy characteristics (low core positivity).
5. Patients with Gleason 4 + 3 = 7 (ISUP grade 3) should be excluded automatically.
6. Patients with PSA > 10 ng/ml should not be excluded automatically; instead, PSA density should be utilised. However, the thresholds for inclusion/exclusion based on PSA density remain uncertain.
7. Patients with cT2b should not be excluded automatically.
8. Patients with ≥ T2c should be excluded automatically.
9. Following targeted and systematic biopsies, the results of targeted biopsies should be reported separately from those of systematic biopsies.
10. Following prostate biopsies, the extent of disease should be reported in length (in mm) or % tumour volume (as a proportion of total volume of core).
11. Following prostate biopsies, the ISUP grade (Gleason sum score) should be reported for each positive core.
12. Following prostate biopsies, percentage of Gleason pattern 4 carcinoma should be provided for each biopsy site with Gleason score 7 carcinoma.
13. Patients with intraductal and cribriform histology on biopsy should be excluded automatically.
14. When systematic biopsies are performed, the extent of disease based on histological characteristics (eg, core length, core volume, core positivity, etc.) should be reported, as it influences the inclusion and exclusion criteria.
15. Patients with Gleason 3 + 3 = 6/ISUP grade 1 disease should be excluded if they have a high extent of disease on histology. However, the definition of "high extent" remains uncertain.
16. There is no need for confirmatory biopsies if upfront mpMRI followed by systematic and targeted biopsies has been performed.
17. If targeted biopsies based on mpMRI images have been performed, the number of positive cores should not be used as an indicator of the extent of disease or tumour volume. Instead, the number of positive sextants based on systematic and/or targeted biopsies should be considered an indicator of tumour volume.
18. The volume of the dominant lesion seen on mpMRI (PI-RADS V2 ≥ 3) should be considered an indicator of tumour volume.
19. For inclusion, prostate biopsies should be performed by mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies.
20. Patients with ≤ T2 disease should not be excluded automatically on the basis of disease aggressiveness (eg, low ADC values) based purely on mpMRI characteristics.
21. Perform mpMRI at some point for inclusion.
Monitoring and follow-up criteria
22. During active surveillance, men should have their PSA checked every 6 mo.
23. During active surveillance, men should have a DRE every 12 mo.
24. During active surveillance, repeat biopsy should be performed if there is a change in mpMRI (ie, increase in PI-RADS score, lesion volume, or radiological T stage), or by DRE progression or PSA progression. However, it remains unclear whether repeat biopsy should be performed in the absence of any triggers (ie, protocol mandated).
25. If repeat biopsies are needed, they should be performed by mpMRI-guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies. However, it remains unclear when mpMRI should be performed during monitoring, and whether it should be performed routinely or triggered (eg, by PSA or DRE changes.
26. Active surveillance should only be continued in patients if their life expectancy continues to be ≥10 yr.
Reclassification criteria (ie, leaving active surveillance for an active treatment)
27. Reclassification should apply only to patients with life expectancy of ≥10 yr at the time of assessment.
28. Consider reclassifying patients if they develop anxiety or depression due to prostate cancer.
29. Consider reclassifying patients if they are reluctant to undergo repeat biopsies or repeat imaging.
30. Patients should not be reclassified automatically based on PSA progression (including level of PSA, PSA kinetics, or PSA density) alone in the absence of other factors. PSA progression should lead to reclassification only if accompanied by changes in histology on repeat biopsy (ie, upgrade in Gleason sum score/ISUP grade).
31. Patients should not be reclassified automatically based on histological changes showing an increase in disease extent (eg, core positivity, % involvement of core, etc.) as the sole criterion.
32. Patients should not be reclassified automatically based on DRE showing an increase in clinical stage to cT2a or cT2b as the sole criterion.
33. Patients should not be reclassified automatically based on radiological evidence of disease progression as the sole criterion. Instead, radiological evidence of progression mandates an image-directed biopsy and patients are reclassified only if it confirms upgraded disease.
34. Patients should not be reclassified automatically based on a new focus of cancer shown on repeat imaging; instead, they should be reclassified only if image-directed biopsy confirms upgraded disease.
35. Patients should not be reclassified automatically based on an increase in tumour volume (for ≤ T2 disease) on imaging alone (ie, in the absence of rebiopsy, PSA, etc.); instead, this mandates an image-directed biopsy and patients are reclassified only if it confirms upgraded disease.
36. Patients should not be reclassified automatically based on an increase in the PI-RADS score as the sole criterion.
37. Consider reclassifying patients if they choose to undergo active treatment, independent of other factors.
Outcome measures that must be prioritised
38. The following outcome measures should be prioritised in all protocols of deferred active treatment:
Overall survival
Prostate cancer–specific survival
Progression to metastatic stage
Local progression
Symptomatic progression
Reclassification
Urinary function
Sexual function
Overall quality of life
Anxiety
Depression

ADC = apparent diffusion coefficient; DRE = digital-rectal examination; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

reflects contemporary practice, whereby patients within DAT programmes are managed mostly by urologists. Additionally, there was an unusually high attrition rate within the patient group between rounds 1 and 2 of the Delphi survey (41%). However, the outcome of all statements rated by patients remained stable between rounds 1 and 2, hence suggesting that the attrition had minimal impact on the consensus outcome. There is also a small risk of introducing sampling error in terms of failure to achieve a balance between contrasting attitudes regarding active surveillance. However, through purposive sampling of a large number and a wide range of clinical practitioners involved in active surveillance, diverse opinions regarding active surveillance would have been achieved and hence minimising this risk.

The choice of a threshold for defining consensus (ie, 70% in our study) merits a brief discussion. It may be argued that

this is an arbitrary figure. However, our decision to use this threshold was informed by the methodological literature and through experience in previous consensus research conducted by members of the project steering group [12,13,18]. Many consensus projects define consensus as ≥70% of the participants choosing scores 7–9 and <15% choosing scores 1–3 (or vice versa) on a 9-point Likert scale, in order to account for the majority opinion whilst not dismissing divergent opinions [10,11,19]. The major emphasis in consensus methodology resources is that any threshold must have been judiciously selected, justified, and described a priori [20,21]. A higher threshold of 80% or 90% gives undue influence to outlier opinions and would have significantly reduced the number of items reaching consensus, which seriously impairs the study's usefulness in clinical practice and research.

Lastly, the study did not achieve consensus on all statements, with 36 items (28%) failing to reach consensus, although 24 items from this group (ie, 67% out of the total number of statements not reaching consensus) achieved near consensus (Table 8). This reflects persisting uncertainty even amongst experts and specialists in the field, which can be resolved only through assessment of robust data from comparative studies from which higher levels of evidence can be obtained.

4.4. *Areas for further research*

We highlight persisting uncertainly and areas for further study. Firstly, for DAT eligibility, there is a need to improve determination of life expectancy more accurately and on an individualised basis. Presently, a combination of approaches and strategies are employed, but they apply on a general rather than an individual level. A potential way forward may include studies exploring the creation of nomograms or actuarial tables integrating essential elements influencing life expectancy, such as age, ethnicity, social class, occupation, family history, specific comorbidities, smoking status, and so on. Secondly, as our project has shown, certain thresholds remain contentious. For instance, thresholds beyond which disease extent on biopsy ought to lead to exclusion of patients with low-risk disease, or the role of mpMRI in determining disease stage and aggressiveness as a criterion for inclusion or exclusion into DAT programmes, require data from prospective, well-designed studies, incorporating diagnostic accuracy elements and allowing synthesis of evidence regarding clinical effectiveness. In particular, the definition of "high disease extent" based on biopsy characteristics remains problematic, although there was consensus on its importance. The role of a negative confirmatory biopsy was also not adequately explored in our study, and hence it deserves further study. In addition, since decision making for clinicians and patients regarding DAT should be individualised, there is a need to better understand how the complex interaction between multiple factors influences decision making, especially in terms of relative weighting placed on different variables and their trade-offs; this could be explored through studies utilising discrete choice experiments [22]. In terms of monitoring and follow-up, there was no consensus regarding the role of per-protocol mpMRI or per-protocol repeat biopsies (ie, untriggered), or on their frequency and timing. The lack of consensus on the need for protocol-mandated (ie, untriggered) repeat biopsies is particularly striking because many contemporary prospective studies on DAT include them. Although we found consensus regarding repeat biopsy being required if there was a change in mpMRI, digital rectal examination progression, or PSA progression, it has to be acknowledged that the sensitivity of these triggers for higher-grade disease remains unproven. The evolving role of mpMRI in detecting clinically significant disease in place of biopsy is promising, as are new biomarkers (reviewed in the study of Loeb et al [23]), including serum markers (eg, Prostate Health Index and 4 K score), urinary markers (eg, Prostate Cancer Antigen 3, or PCA3), and tissue markers (eg, genomic profiling). Once data on these promising diagnostic interventions mature, future studies should integrate them into nomograms predicting the probability of reclassification. In addition, given the current heterogeneity in practice, there is a need to standardise the risk categories and follow-up strategies in large prospective studies. Lastly, the findings from our study will improve and direct the standardisation of undertaking DAT in routine clinical practice and research. Clinicians should use them to carefully design their DAT protocols such that comparative clinical effectiveness data can be prospectively collected and the results audited regularly. Researchers should follow our guidance, and perform clinical trials or prospective cohort studies comparing different DAT protocols against each other and against immediate curative interventions.

5. Conclusions

The EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel, in partnership with other leading guideline authorities and patient advocacy organisations (Supplementary material), undertook an ambitious project using a novel and transparent approach in this setting to develop consensus statements for all domains relating to DAT, to standardise clinical practice and research. Protocol-driven, robust, and transparent methods were utilised. Consensus was achieved on 93 out of 129 statements (72%), covering the domains of criteria for patient selection, inclusion and exclusion (including patient and disease characteristics, imaging criteria, and type of biopsies), nature and timing of investigations and assessments during the period of monitoring and follow-up (including PSA measurements, clinical examination, repeat imaging and repeat biopsies), criteria and thresholds for reclassification and change in management, and type of outcome measures that should be prioritised. The findings will guide and inform routine clinical practice and research by being incorporated into guidelines issued by the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel and partner organisations, until higher levels of evidence emerge through prospective comparative studies and clinical trials.

Author contributions: Thomas B.L. Lam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lam, MacLennan, Willemse, Mason, Cornford, Mottet.
Acquisition of data: Willemse, Donaldson, Davis, Dell'Oglio, Fankhauser, Grivas, Ingels, Lardas, Liew, Pang, Paterson, Omar, Zattoni, Buddingh.
Analysis and interpretation of data: Lam, MacLennan, Willemse, Mason, Cornford, Mottet.
Drafting of the manuscript: Lam, MacLennan, Willemse.
Critical revision of the manuscript for important intellectual content: Plass, Shepherd, Baanders, Bangma, Bjartell, Bossi, Briers, Briganti, Buddingh, Catto, Colecchia, Cox, Cumberbatch, Davies, Davis, De Santis, Dell'Oglio, Deschamps, Donaldson, Egawa, Fankhauser, Fanti, Fossati, Gandaglia, Gillessen, Grivas, Gross, Grummet, Henry, Ingels, Irani, Lardas, Liew, Lin, Moris, Omar, Pang, Paterson, Renard-Penna, Ribal, Roobol, Rouprêt, Rouvière, Sancho Pardo, Richenberg, Schoots, Sedelaar, Tilki, Lauridsen, van den Bergh, Van den Broeck, van der Kwast, van der Poel, van Leenders, Varma, Violette, Wallis, Wiegel, Wilkinson, Zattoni, N'Dow, Van Poppel.
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Bjartell is a company consultant for Astellas and Janssen; receives speaker honorarium from Astellas, Janssen, IPSEN, Bayer, and Ferring; participates in trials run by Astellas, Janssen, Pfizer, Ferring, and Myovant; received travel grants from Astellas, Bayer, Ferring, IPSEN, and Janssen; received research support from Astellas, Ferring, and Bayer, and financial compensation as Senior Consulting Editor of *European Urology*; and holds stock in LIDDS Pharma AB, Glactone Pharma AB, and WntResearch AB. Professor Dr. A. Bossi is the head of the GU Unit at the Radiation Oncology Department of the Gustave Roussy Institute, Villejuif, France; is a company consultant for Sanofi and Astellas; receives company speaker honorarium from IPSEN, Janssen, and Astellas; and is a co-principal investigator for the PEACE 1 trial run by UNICANCER. Dr. E. Briers has received grant and research support from IPSEN, the European Association of Urology, and Bayer; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Professor Dr. A. Briganti is a company consultant for Astellas, Janssen, Opko Health, MDx Health, and Bayer; received company speaker honorarium from Astellas and Ferring; and received research support from Sandoz. Professor Dr. J. W.F. Catto received company consultant honoraria from Steba Biotech, AstraZeneca, Merck Sharp & Dohme, BMS, and Nucleix Ltd. Dr. B.W. Cox declares an equity interest in C4 Imaging, LLC. Professor Dr. M. 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Rouprêt is a company consultant for Lilly, GSK, Ipsen, Astellas, Takeda, Sanofi Pasteur, and Medac; received research support from GSK, Pfizer, and Roche; and received speaker honorarium from Roche and Zambon. Professor Dr. D. Tilki received speaker honorarium from Astellas and a travel grant from Janssen. Professor Dr. H.G. van der Poel is a company consultant for Intuitive Surgical; has participated in trials for Astellas and Steba Biotech; and has received grant and research support from Astellas. Professor Dr. G.J.L.A. van Leenders has served on the advisory board for Roche, and received company speaker honorarium from Astellas and research grants from Roche and AstraZeneca. Professor Dr. P.D. Violette received company speaker honoraria from Janssen and Sanofi. Professor Dr. T. Wiegel is an advisory board member for IPSEN; receives company speaker honoraria from IPSEN and Hexal; is a member of the Janssen Steering Committee; and has participated in the ATLAS/AUO trial. Dr. F. Zattoni holds a patent for "Sign In Indirect visualization-assisted apparatus and method for positioning medical instruments" European Patent Office (Grant number EP3261551A1. Entity holder: FABER IND SpA, Faber Industrie SpA). Professor Dr. P. Cornford is a company consultant for Astellas, IPSEN, and Ferring; receives company speaker honoraria from Astellas, Janssen, IPSEN, and Pfizer; participates in trials run by Ferring; and receives fellowships and travel grants from Astellas and Janssen. Professor Dr. N. Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring; and has received fellowships and travel grants from Astellas, IPSEN, Sanofi, Janssen, and Roche. Dr. S. MacLennan,

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Appendix A. Supplementary data

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