Brief Correspondence

Study protocol for DETECTIVE Study: An international collaborative study to develop consensus statements for deferred treatment with curative intent for localised prostate cancer

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1360 Words

Abstract:

Deferred active treatment (DAT) strategies, including active surveillance and active monitoring, are a recognised management option for men with localised low-risk prostate cancer. However, because of heterogeneity in the literature, there are uncertainties regarding the optimum criteria for patient selection, and the optimum constitution and scheduling of follow-up, monitoring characteristics, reclassification thresholds, and which outcome measures should be prioritised. This protocol describes a study led by the European Association of Urology (EAU) Prostate Cancer Guidelines Panel in conjunction with other guideline organisations and patient

advocacy groups* to develop consensus statements for all domains of deferred active treatment. The project is divided into 3 sequential phases: (1) Systematic review of studies reporting on DAT in order to summarise and define range of heterogeneity regarding all domains; (2) Two-round Delphi online survey involving a large, international multidisciplinary panel of healthcare professionals (HCPs) and patients to initiate consensus; and (3) Consensus group meeting involving representatives from HCP and patient stakeholder groups to finalise the consensus process. The consensus statements are expected to be adopted by clinical practice guidelines in order to standardise and guide practice for clinicians and researchers until better evidence emerges.

Patient summary: We describe a project aimed at standardising elements of practice in active surveillance/monitoring for early localised prostate cancer, because currently there is great variation and uncertainty regarding how best to conduct them. This will be achieved through a structured process of agreement (i.e. consensus) amongst a large, international panel of healthcare professionals and patients.

Deferred active treatment (DAT) strategies for men with localised prostate cancer have emerged as a viable alternative to radical intervention as we aim to avoid the consequences of over-treatment. Nevertheless, such strategies remain controversial, with significant uncertainty and heterogeneity in all domains, including criteria on patient selection, nature and timing of interventions during follow-up, criteria and thresholds for reclassification, and which outcome measures should be prioritised[1-3]. These are important barriers to the conduct and uptake of DAT by clinicians and patients as they prohibit the comparison of the clinical effectiveness of different protocols. In order to address these issues in a comprehensive, robust and systematic manner, the EAU Prostate Cancer Guidelines Panel, in partnership with other leading guideline authorities and organisations*, has commissioned a project to develop consensus statements in all domains relating to DAT in order to standardise clinical practice and research.

The specific objectives are to achieve consensus on the following domains: (1) Criteria on patient selection (including patient and disease characteristics, imaging criteria and type of biopsies); (2) Nature and timing of investigations and assessments during follow-up (such as repeat imaging and repeat biopsies); (3) Criteria and thresholds for reclassification; and (4) Type of outcome measures which should be prioritised.

To address these objectives, we will utilise transparent consensus methods involving a large, international cohort of stakeholders, broadly divided into two groups: (1) Healthcare professionals (HCPs) consisting of urologists, clinical or radiation oncologists, medical oncologists, radiologists, pathologists, primary care physicians, and nurse specialists; and (2) Patients. The research will be divided into 3 distinct but inter-related phases, and is expected to last 12 months.

Phase 1 is a systematic review conducted according to PRISMA guidelines[4]. The aim is to describe, explore and assess clinical heterogeneity in DAT studies which will inform the statements for the consensus processes. The review protocol has been published[5]. In brief, all prospective single-arm case series of DAT (including active surveillance and active monitoring but excluding watchful waiting), and all prospective comparative studies involving DAT will be included. The review will summarise eligibility and selection criteria, characteristics of monitoring and follow-up (including the type, frequency and timing of repeat imaging and repeat biopsies), reclassification definitions and thresholds, and primary outcomes measured in studies. English language articles published after 1990 will be included. Summary of

findings tables including details of the pre-specified domains and sub-domains will be developed. From these tables, a list of statements organised according to the different domains and sub-domains relating to all aspects of DAT will be generated.

Phase 2 will comprise of a two-round online Delphi survey involving a large, international cohort of key stakeholders (HCPs and patients). The consensus methods used have been described previously in consensus studies in prostate cancer[6,7]. HCPs involved with DAT identified through international specialist societies* will be invited to participate. Patients throughout Europe with localised prostate cancer and eligible for DAT will be recruited through patient advocacy organisations*. Up to 150 HCPs and 50 patients will be invited to participate. Patients will be asked to complete the patient-relevant parts of the survey only (i.e. identification of most important outcomes). Participants will be asked to vote based on their level of agreement, on a nine-point scale, ranging from strongly disagree (1) to strongly agree (9) (i.e. 1–3 disagree; 4–6 uncertain; 7–9 agree). There will also be an 'Unable to answer' option. An online questionnaire will be developed for the Delphi process using COMET Initiative DelphiManager[8]. Two iterative rounds will be conducted anonymously, with anonymised feedback provided to all participants at the end of each round showing the percent scoring at each response option. In Round 1, participants will have the opportunity to add further statements for incorporation into Round 2. With an anticipated response rate of 80% for both stakeholder groups, and expected overall completion rate of 80%, the total number of participants involved is expected to be at least 128 (i.e. 96 HCPs and 32 patients). The results for each stakeholder group will be analysed and presented separately in each round. After the final round, statements scoring 'strongly agree' (i.e. 7–9) by ≥70% of participants AND with minimal disagreement scored by the rest (defined as <15% of participants scoring 'strongly disagree' i.e. 1-3) will be considered as reaching the threshold for 'consensus agree'. Conversely, statements scoring 'strongly disagree' (i.e. 1-3) by ≥70% of participants AND with minimal agreement scored by the rest (defined as <15% of participants scoring 'strongly agree' i.e. 7-9) will be considered as reaching the threshold for 'consensus disagree'. All other statements not falling in the above categories will be classified as 'equivocal'. Statements reaching consensus (either agree or disagree) will be collated for review in Phase 3, whilst equivocal statements will be brought forward for discussion and voting in Phase 3.

Phase 3 is the final stage of the consensus process, involving a 1-day meeting attended by representatives of each stakeholder group and chaired by a non-voting methodologist and a clinician moderator. We will use structured discussion and live voting sessions. Representatives from each stakeholder groups and sub-groups (i.e. urologists, oncologists, radiologists, pathologists and patients) will be purposively sampled from those completing all rounds of the Delphi survey to ensure proportional representation. The voting panel will consist of 25 voting participants (i.e. 7 patients and 18 HCPs). Statements reaching consensus (either agree or disagree) from Phase 2 will be reviewed by the panel. Consensus decisions from the Delphi survey cannot be overturned by the panel without sound reasoning (e.g. misleading statements). Equivocal statements from Phase 2 will be discussed and voted on by the panel. Scoring thresholds will be the same as Phase 2 (i.e. level of agreement on a nine-point scale: 1–3 disagree; 4–6 uncertain; 7–9 agree; and 'Unable to answer'). Voting will be anonymous using Poll Everywhere[9] which participants can access during the meeting using personal computers and a shared IP address. Definitions of consensus will be the same as in Phase 2. Results for all statements will be conveyed in real-time, and final consensus statements will be prepared. A final list of consensus statements organised according to the domains and sub-domains of DAT will be issued.

The consensus statements are expected to be adopted by guideline developers and disseminated through clinical practice guidelines issued by the EAU Prostate Cancer Guidelines Panel and other organisations*, and are intended to provide authoritative guidance to clinicians and researchers by standardising definitions, thresholds, terminology and characteristics of patient selection, monitoring, reclassification and change in management, and outcome measures which should be prioritised in programmes of deferred active treatment in clinical practice and research, at least until higher levels of evidence emerge such as from the GAP3 initiative[10].

** The list of official collaborators include the following organisations and patient advocacy groups:*

European Association of Urology (EAU)
European Association of Urology Nurses (EAUN)
EAU PIONEER
European Urology Editorial Board
American Urological Association (AUA)
Canadian Urological Association (CUA)
European Society for Radiotherapy and Oncology (ESTRO)
International Society of Urological Pathology (ISUP)
Urological Society of Australia and New Zealand (USANZ)
European Society of Urogenital Radiology (ESUR)
EAU Section of Oncological Urology (ESOU)
Urological Association of Asia (UAA)
American Society for Radiation Oncology (ASTRO)
American Society of Clinical Oncology (ASCO)
European Forum for Primary Care (EFPC)
EAU Research Foundation (EAU RF)
UCAN UK
Tackle Prostate Cancer UK
Europa UOMO
Movember Foundation

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