

Prostate Cancer

Setting an Agenda for Assessment of Health-related Quality of Life Among Men with Prostate Cancer on Active Surveillance: A Consensus Paper from a European School of Oncology Task Force

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Abstract

Background: Literature on the health-related quality of life (HRQoL) for men with localized prostate cancer (PCa) on active surveillance (AS) shows a need for methodological guidance regarding HRQoL issues and how to address them.

Objective: The European School of Oncology Task Force (ESO TF) aimed to identify a core set of research questions and related measures to include in AS HRQoL studies.

Design, setting, and participants: A modified Delphi study was used to reach consensus on AS HRQoL research topics and tools between 2014 and 2015. Data were collected by engaging a multidisciplinary team of 15 experts.

Outcome measurements and statistical analysis: An open-ended questionnaire was used to collect information from ESO TF members regarding issues in AS HRQoL research. Then a structured questionnaire was used to collect ratings on the usefulness/importance of different AS HRQoL aspects. Items that $\geq 80\%$ of ESO TF members rated as useful/important were retained. Items with a 50–80% rating were discussed to reach final agreement.

Results and limitations: Six main research questions concerning the selection of outcome measures, measurement tools, and comparison groups were identified as relevant. The core set of measures identified were related to individual characteristics, psychological dimensions; decision-making-related issues, and physical functioning. The multidisciplinary expertise of ESO TF members was a significant asset, even if bringing different backgrounds to the discussion table represented a challenge.

Conclusions: HRQoL measures have to be sensitive to the specific needs of men on AS. The definition of HRQoL outcomes will enhance a broader understanding of the HRQoL of men on AS and sustain patient-centered medicine.

Patient summary: An international panel agreed on a set of health-related quality-of-life aspects to be assessed among men on active surveillance for prostate cancer. Valid relevant questionnaires were identified. The experts' indications lay a foundation for future research and clinical practice.

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1. Introduction

With international guidelines recommending that active surveillance (AS) should be offered to men with very low-risk/low-risk prostate cancer (PCa) when appropriate, and patients' associations stressing the need to be offered all available options, there has been slow but steady implementation of AS [1,2].

AS reduces the burden of treatment-related side effects, but men may live with greater uncertainty because of the possibility of future reclassification of their cancer [3]. There is still concern about the possible impact of living with untreated PCa on health-related quality of life (HRQoL). Currently available studies do not allow firm conclusions, mainly because of methodological flaws such as lack of comparison group(s), no randomization, and limited follow-up [4,5].

To address such limitations and to provide directions for future AS HRQoL studies, the European School of Oncology (ESO) established an international task force (TF) to address the main issues regarding assessment of AS HRQoL from a multidisciplinary and multiprofessional perspective. This article presents the recommendations of the ESO TF on a core set of HRQoL factors that should be considered for men on AS. Study design criteria are outlined and specific validated questionnaires are described.

2. Materials and methods

A modified Delphi approach was used to establish recommendations for assessment of AS HRQoL. Consensus was achieved after the following six steps (Fig. 1).

- (1) *Kick-off meeting*: A multidisciplinary group of 15 AS experts joined a discussion on AS-related HRQoL issues. The panel included urologists, radiation oncologists, psychologists, a health scientist, a data scientist, project coordinators, epidemiologists, and advocacy group (Europa Uomo) representatives. A group coordinator (L.B.) and a core working group (F.K., T.R., L.V., S.V.) were nominated.
- (2) *Systematic literature exploration*: A background search was conducted to obtain an overview of the methodology used to conduct research on HRQoL among men on AS. A related systematic review was published in 2015 [4].
- (3) *Round 1*: An open-ended questionnaire was mailed for first collection of suggestions regarding what aspects measurement of HRQoL for men on AS should include and how it should be conducted. Two versions were used: (1) one for researchers already conducting AS HRQoL assessment and (2) one for ESO TF members not directly involved in research, such as patient association members and some clinicians. The group coordinator reviewed and summarized the responses.
- (4) *Round 2*: In the second round, ESO TF members were asked to rate the usefulness or importance of aspects concerning AS HRQoL measurement (outcome measures, measurement tools, control groups, and timing of assessment) derived from round 1. A survey of 63 items using a 4-point Likert scale (from "not useful" to "very useful") was developed. Data collection was anonymous. Twelve out of 15 (80%) TF members returned the opinion survey. Items rated useful and/or important for inclusion in AS HRQoL assessment by <50% of respondents were excluded; items rated useful and/or important by 80–100% of respondents were included as recommendations; items rated as useful and/or important by 50–80% of respondents were

considered as topics for further discussion. During this round, agreement about inclusion or exclusion was reached for 25/63 items (21 items included, 4 excluded). These thresholds were specified a priori. Agreement at 80–100% is related to agreement at a level of qualified majority. Agreement at a level of absolute but not qualified majority led to further discussion in the face-to-face meeting.

- (5) *Round 3*: Experts participated in a face-to-face meeting in Madrid during the European Association of Urology annual meeting to discuss the aspects of AS-related HRQoL assessment that had reached an agreement level of 50–80% (38 items); 13/15 of the TF members attended this meeting. The issues mainly discussed were the types of questionnaire to use on the basis of their validity and generalizability, and on avoiding patient burden in completing them. A further topic of discussion was the importance of identifying research questions that also had clinical implications in the sense of support for patients in the decision-making process on whether or not to opt for AS.
- (6) *Round 4*: Decisions on selected methodological issues that were not resolved from round 3 were left to the core working group given their expertise with the specific HRQoL measurement tools.

3. Results

A core set of AS HRQoL outcomes resulted from the consensus process, together with adequate standardized measurement tools to evaluate such outcomes (Table 1). Suggestions regarding assessment timing were also provided (Fig. 2).

3.1. How to measure HRQoL for men on AS

HRQoL ranges from the individual perception of health status and ability to function in life to subjective evaluation of the extent to which physical, emotional, and social well being may be affected by a medical condition or its treatment [6].

Since disease-specific and generic HRQoL areas may influence each other in PCa, the ESO TF suggested a broad evaluation. It was agreed (83%) to use the Short Form 36 (SF-36) questionnaire or the abbreviated 12-item version (SF-12) [7,8] to measure generic HRQoL. In addition, use of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire was suggested as a PCa-specific tool [9].

3.2. Association of patient characteristics with AS HRQoL

Understanding how individual features may impact acceptance and adherence to AS could support clinicians and patients to reach a shared decision. TF members (>80%) agreed that demographic characteristics (age, marital status, education, working status), comorbidities, and personality traits should be assessed.

It has been found that age, marital status, and education are predictors of HRQoL among men on AS [10]. In fact, younger men on AS may be more anxious about missing the window of opportunity for radical curative treatment. The presence of a partner or spouse may offer support to men, but may also trigger the decision to switch to a radical treatment. The ESO TF group suggested that the view of

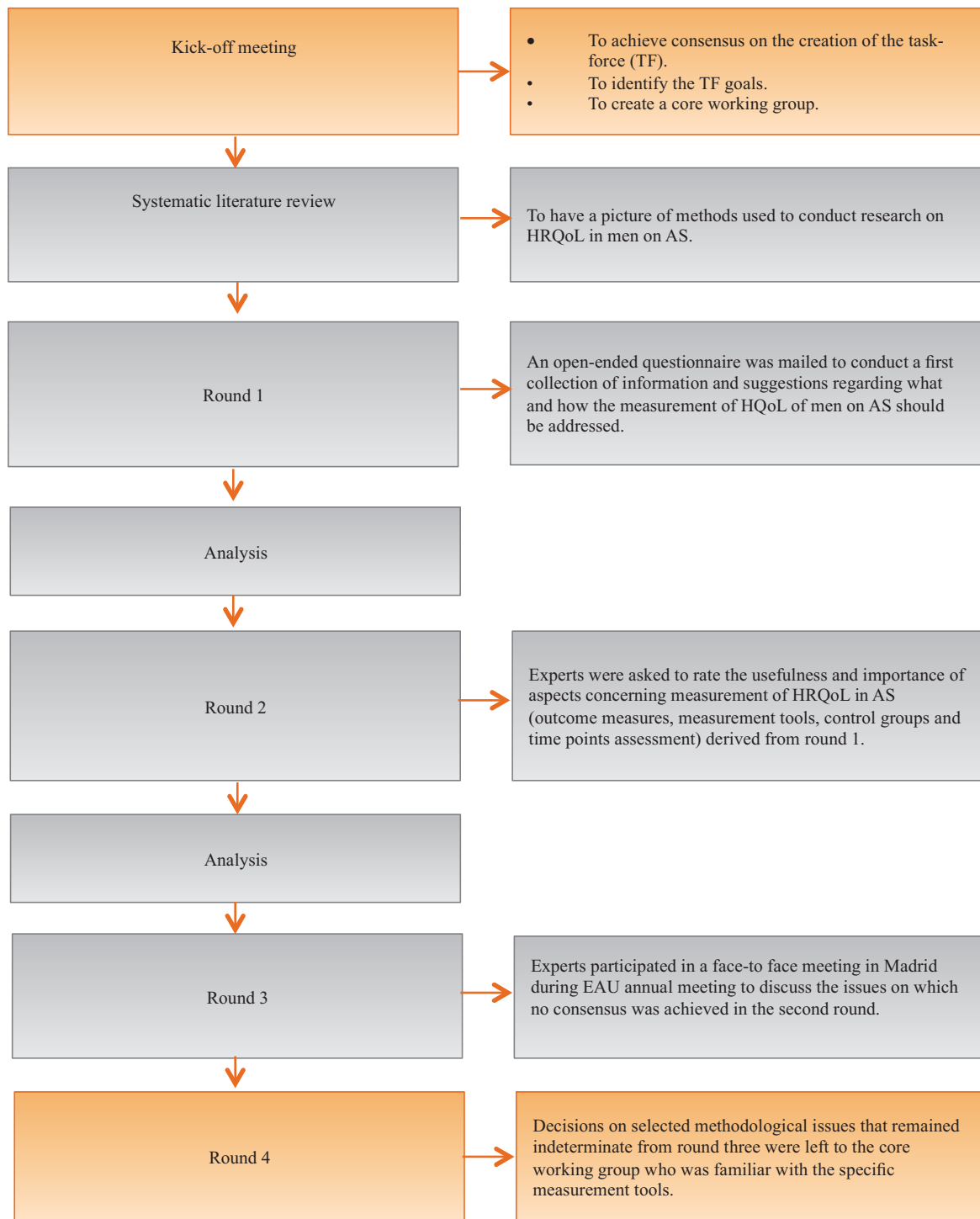


Fig. 1 – Taskforce flowchart. AS = active surveillance; HRQoL = health-related quality of life.

partners should be sought when proposing AS to facilitate a shared decision. Level of education should be considered because the assumption that men with higher levels of education can more effectively process AS-related medical information is widespread, but still not supported by evidence.

Comorbidities should be recorded as a potential confounding variable for HRQoL, via either validated questionnaires (eg, the Self-administered Comorbidity Questionnaire [11]) or ad hoc interviews.

Personality characteristics are associated with PCa-related coping, HRQoL, and decisional regret [11]. TF

Table 1 – Summary of the research questions identified as relevant to consider when tracking health-related quality of life among men with prostate cancer on active surveillance (AS) and the final core set of factors and measures prioritized by the Delphi panel

Research question	Features	Suggested tool
1. Health-related quality of life		SF-12/SF-36
2. Patient-related characteristics	Age	FACT-P
	Education	Interview
	Marital status	Interview
	Employment status	Interview
	Comorbidities	SCQ/interview
3. Psychological dimensions	Personality	EPQ-R
	Generic anxiety	STAI
	PCa-specific anxiety	MAX-PC
	Coping	Mini-MAC
4. Decision-making-related process	Depression	PHQ-2
	Reasons for not choosing AS	Interview
	Reasons for choosing AS	Interview
	Reason for stopping AS	Interview
	Decision conflict	Decisional Conflict Scale
	Partners' preferences	Interview
5. Physical functioning	Social support	Social Wellbeing Scale (FACT-P), MSPSS
	Regret	Decisional Regret Scale
	Erectile function	IIEF
6. Comparison group	Urinary function	IPSS
	Men with PCa diagnosis eligible for AS but chose radical treatment (RP, ERT, BT)	
	Men who underwent focal therapy	
	Men who chose AS but were later advised to quit AS owing to disease reclassification or progression and received radical treatment	

BT = brachytherapy; EPQ = Eysenk personality scale; ERT = external radiation therapy; FACT-P = Functional Assessment of Cancer Therapy-Prostate; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; MAX-PC = Memorial Anxiety Scale for Prostate Cancer; Mini-MAC = Mini-Mental Adjustment to Cancer; MSPSS = Multidimensional Scale of Perceived Social Support; PCa = prostate cancer; PHQ-2 = Patient Health Questionnaire-2; RP = radical prostatectomy; SCQ = Self-administered Comorbidity Questionnaire; SF-36/12 = Short Form 36/12; STAI = State Trait Anxiety Inventory.

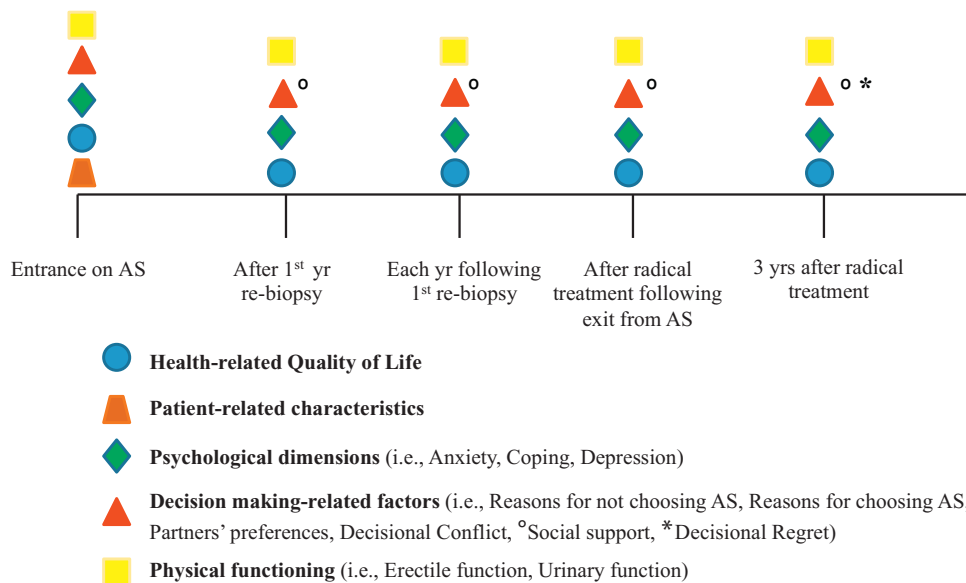


Fig. 2 – Suggested timeline for data collection.

members agreed (90%) to consider personality as a factor that may impact AS-related HRQoL. The decision for the assessment tool was left to the core group, who recommended use of the abbreviated form of the Revised Eysenk Personality Questionnaire [12].

3.3. Effect of psychological dimensions on HRQoL among AS patients

Anxiety and depression as indicators of psychological burden as well as coping with cancer were rated as the

most important psychological dimensions to address in AS HRQoL studies.

3.3.1. Anxiety

Anxiety as a result of living with untreated PCa may represent a significant problem. The majority of men who opted for AS reported low levels of anxiety in the short term [4]. Reported rates of anxiety above a clinical threshold show large variation, ranging from 1–2% [13] to 23% [14]. Men with heightened anxiety are more likely to switch to radical treatment in the absence of medical reasons [15–17].

The TF (92%) included anxiety as an important factor in AS-related HRQoL. For assessment of both generic and disease-specific anxiety, the State Trait Anxiety Inventory (STAI) and the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) were recommended. The STAI differentiates between a temporary condition of state anxiety and a more general and longstanding dimension of trait anxiety [18]. The MAX-PC provides a brief and effective measure of anxiety specifically related to PCa [19].

3.3.2. Depression

The body of literature on depression among cancer patients has increased exponentially, but very few studies have addressed depression among men on AS. In these studies, scores for men on AS were low [4] and did not change over time [17]. Owing to its huge impact on HRQoL, the ESO TF recommended (80%) measurement of depression. So far, studies on AS have used the Center for Epidemiological Studies Depression Scale, the Hospital Anxiety and Depression Scale, and the nine-item depression scale of the Patient Health Questionnaire (PHQ-9). The core group considered the two-item short version of the PHQ as the most user-friendly for an initial screening [20].

3.3.3. Coping with AS

Coping strategies may have an important impact on HRQoL during cancer management. So far, only one study has addressed the role of coping in AS [4]. The TF (100%) agreed on considering coping with cancer as an influential factor and recommended the Mini-Mental Adjustment to Cancer scale [21].

3.4. Decision-making between AS and curative treatments

One of the factors that may influence HRQoL of men on AS is how they choose between radical treatment and AS [11]. When men were asked which were the most important advantages of AS, the predominant answers were related to delaying the side effects of radical therapies [22,23]. Disadvantages reported were the risk of unfavorable consequences (eg, progression and metastases) and the distress associated with that risk. The TF members recommended addressing the reasons for choosing (83%) or not choosing AS (91%) to facilitate a shared decision.

Uncertainty about which action to take can be a psychological stressor, and addressing the potential conflict in the decision-making process may be of great value in clinical practice. However, the TF did not unanimously

agree (70%) on recommending inclusion of assessment of decisional conflict (DC) in the core outcome set. Given that higher DC is associated with lower patient adherence to and satisfaction with the choice, discussion among core group experts resulted in a suggestion to include evaluation of DC as a factor potentially influencing HRQoL. The validated Decisional Conflict Scale [24] was recommended for DC assessment.

Since DC may lead to a sense of regret in the post-treatment phase, the TF agreed (83%) on evaluating this issue. The Decision Regret Scale, a validated tool available for this purpose [25], was recommended by the core group.

The TF agreed on investigation of family and social support (90% agreement) given their influence on decision-making and HRQoL [11]. The final recommendation by the core group was to adopt the Social Wellbeing Scale of the FACT-P or a more specific tool such as the Multidimensional Scale of Perceived Social Support to assess an individual's perception of social support [26].

Since 20% of patients on average choose to stop AS in the absence of a clinical recommendation but because of anxiety or personal choice [27], TF members suggested (100%) collection of the individual reasons underlying these cases. This information may be useful in addressing the causes, such as possible cancer-related anxiety, to improve future retention rates.

3.5. Physical functioning

Even in the absence of PCa-related symptoms, assessment of different physical functional issues, such as urinary and erectile functions, is recommended (91%) because they could be impaired in relation to age and invasive procedures used for PCa monitoring (ie, repeated biopsies) [28]. No unanimous agreement (50–80%) was reached regarding any of the measurement tools available: the Sexual Health Inventory for Men (SHIM), the 5-item version of the International Index of Erectile Function (IIEF-5), the Expanded Prostate Cancer Index Composite (EPIC), and the International Prostate Symptom Score (IPSS). The core working group suggested use of the IPSS [29], which evaluates urinary symptoms specifically related to the prostate, and IIEF-5 [30], which was preferred to SHIM since a greater percentage of the TF members were familiar with it (81% for IIEF-5 vs 50% for SHIM). EPIC was indicated as a second choice because it focuses more on treatment side effects rather than on impairment of normal functioning.

3.6. Clinically relevant cohorts for comparison of HRQoL for men with localized PCa in AS

Up to now, studies have compared HRQoL outcomes for men on AS with the general male population and those who have undergone radical treatment [5].

The TF identified three cohorts of interest for comparison with men on AS:

- (1) Men with a PCa diagnosis who were eligible for AS but chose radical treatment to minimize the hazard of progression (100% consensus).

- (2) Men who have undergone minimal invasive focal therapy (attentively identified), which entails the risk of a misclassified disease at diagnosis (92% consensus).
- (3) Men who chose AS but were later advised to quit AS owing to disease reclassification or progression and received radical treatment (83% consensus).

4. Discussion

The ESO TF experts contributed with their different expertise to the definition of a core set of research issues that need to be addressed when evaluating HRQoL among men with PCa on AS. Men with low-risk indolent PCa who choose AS face the peculiar challenge of being diagnosed with cancer and not immediately (potentially never) being treated for their disease. Therefore, assessment of HRQoL has to be tailored to this specific population. For this reason, it is important to identify specific outcomes and to measure them using validated tools.

The main results of the consensus are that: (1) fundamental aspects of AS HRQoL deal with overall self-perception of well being, professional and physical functioning, and family role; (2) anxiety and depression represent the two main psychological consequences of cancer diagnosis and recurrence, and thus need to be taken into account; and (3) the patient decision-making process between active treatment and observational strategies has to be clear to both the patient and clinician, because this information may support men in coming to a decision that is satisfactory in the short and long run.

Implementation of the recommendations presented in this paper will allow consistent data collection. Researchers could choose, among the suggestions, which AS HRQoL issues to address while taking into account the feasibility and time required for an average patient to complete the related questionnaires. A preliminary overall cost-effectiveness evaluation should be conducted and should take into account how much information the study adds to what has already been properly investigated. Moreover, researchers will need to identify which tools are validated in the patient's native language.

A preliminary trial should also be conducted to assess the cognitive, emotional, and time burdens for patients when completing the questionnaires. Comparison of results from different populations across the world will become feasible, and could eventually lead to a better and broader understanding of the HRQoL of men on AS.

The different knowledge and expertise that ESO TF members brought to the table represented an incredible asset throughout the consensus process. Nonetheless, these differences led to some difficulties. In particular, differences in familiarity with the assessment tools between clinicians and research psychologists required thorough discussion before reaching agreement. Sharing the common aim of addressing HRQoL issues in AS from both a clinical and a research point of view, all the ESO TF members made an effort to go beyond the boundaries of their specialty field and their comfort zone, which provides an important example of a multidisciplinary approach. Establishment of

the TF and the work conducted to achieve its aim represent an approach that should be implemented when designing research on AS HRQoL: collaborative, open-minded, evidence-based, thought-provoking research. It is reasonable to think that more work is still required to address the limitations of the findings reached by the TF. It is desirable to continue such collaborative work and determine the opportunity to discuss with other clinicians and researchers all over the world who are expert in AS, and in the assessment of QoL, what emerged from the TF.

5. Conclusions

This work offers conceptual and methodological suggestions that could be useful in both research and clinical practice for men diagnosed with PCa. Implementation of these suggestions in different cultures will allow the urooncologic community to gain a better understanding of how men face living with an untreated cancer and to design assessment and ad hoc counseling interventions to support AS-eligible men and their families.

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Study concept and design: Bellardita, Rancati.

Acquisition of data: Villa, Bellardita.

Analysis and interpretation of data: Villa, Venderbos, Kendel.

Drafting of the manuscript: Villa, Bellardita, Kendel, Venderbos, Rancati.

Critical revision of the manuscript for important intellectual content: Bangma, Carroll, Denis, Klotz, Korfage, Lane, Mastris, Rannikko, Roobol, Trock, Van den Bergh, Van Poppel, Valdagni.

Statistical analysis: Villa, Rancati.

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Supervision: Bellardita, Valdagni.

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