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European Association of Urology

EUO Priority Article – Prostate Cancer

Standardising the Assessment of Patient-reported Outcome Measures in Localised Prostate Cancer. A Systematic Review

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Article info

Article history:
Accepted October 15, 2021
Available online 14 November 2021

Associate Editor:
Gianluca Giannarini

Keywords:
Prostatic neoplasms
COSMIN
Patient-reported outcome measures
Quality of life
Erectile dysfunction

Abstract

Context: Prostate cancer (PCa) is the second most common cancer among men worldwide. Urinary, bowel, and sexual function, as well as hormonal symptoms and health-related quality of life (HRQoL), were prioritised by patients and professionals as part of a core outcome set for localised PCa regardless of treatment type.

Objective: To systematically review the measurement properties of patient-reported outcome measures (PROMs) used in localised PCa and recommend PROMs for use in routine practice and research settings.

Evidence acquisition: The psychometric properties of PROMs measuring functional and HRQoL domains used in randomised controlled trials including patients with localised PCa were assessed according to the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) methodology. MEDLINE and Embase were searched to identify publications evaluating psychometric properties of the PROMs. The characteristics and methodological quality of the studies included were extracted, tabulated, and assessed according to the COSMIN criteria.

Evidence synthesis: Overall, 27 studies evaluating psychometric properties of the Expanded Prostate Cancer Index Composite (EPIC), University of California-Los Angeles Prostate Cancer Index (UCLA-PCI), European Organisation for Research and Treatment

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https://doi.org/10.1016/j.euo.2021.10.004

Localised prostate cancer

of Cancer (EORTC) quality of life core 30 (QLQ-C30) and prostate cancer 25 (QLQ-PR25) modules, International Index of Erectile Function (IIEF), and the 36-item (SF-36) and 12-item Short-Form health survey (SF-12) PROMs were identified and included in the systematic review. EPIC and EORTC QLQ-C30, a general module that assesses patients' physical, psychological, and social functions, were characterised by high internal consistency (Cronbach's α 0.46–0.96 and 0.68–0.94 respectively) but low content validity. EORTC QLQ-PR25, which is primarily designed to assess PCa-specific HRQoL, had moderate content validity and internal consistency (Cronbach's α 0.39–0.87). UCLA-PCI was characterised by moderate content validity and high internal consistency (Cronbach's α 0.21–0.94). However, it does not directly assess hormonal symptoms, whereas EORTC QLQ-PR25 does.

Conclusion: The tools with the best evidence for psychometric properties and feasibility for use in routine practice and research settings to assess PROMs in patients with localised PCa were EORTC QLQ-C30 and QLQ-PR25. Since EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25 module.

Patient summary: We reviewed and appraised the measurement properties of patient-reported outcome measure questionnaires used for patients with localised prostate cancer. We found good evidence to suggest that two questionnaires (EORTC QLQ-C30 and QLQ-PR25) can be used to measure urinary, bowel, and sexual functions and health-related quality of life.

Introduction

Prostate cancer (PCa) is the second most common solid cancer and the fifth leading cause of cancer death among men worldwide [1]. PCa is characterised by a relatively long natural history, and a substantial proportion of patients die from causes other than the disease itself [2]. Therefore, assessment and monitoring of treatment-related side effects and of health-related quality of life (HRQoL) play a major role in the management of PCa patients. Although metastasis-free and overall survival represent the main outcomes when assessing the efficacy of therapeutic approaches, there is increasing awareness of the importance of measuring what were previously regarded as softer outcomes, namely, side effects and HRQoL, using patient-reported outcome measures (PROMs) [3]. This is crucial when considering that cancer patients may have the possibility of trading HRQoL for length of life [4].

Several PROMs have been proposed and are currently used for assessing different domains (ie, urinary, sexual, and bowel function) and QoL in localised PCa. However, the validity of these tools has been poorly addressed so far and limited data are available on the appropriate PROMs that should be adopted in prospective studies and randomised controlled trials (RCTs). Moreover, a systematic comprehensive assessment of the psychometric properties of PROMs for patients with localised PCa is still missing. PIONEER is a European network of excellence for big data in PCa and is part of the Innovative Medicine Initiative "Big Data for Better Outcomes" programme [5]. The overall aim of PIONEER is to improve PCa care across Europe through the application of big data analytics [5]. One of the many PIONEER objectives was further development of the core outcome set (COS) for localised PCa [6]. Consensus on recommendations for the definitions and measures of clinician-reported outcomes has been completed by the PIONEER Consortium. The patient-reported outcomes that are the focus of this paper are overall QoL, hormonal symptoms, sexual function, urinary function, bowel function, stress urinary incontinence, and faecal incontinence, as previously defined [6].

The aim of this systematic review was to critically appraise, compare, and summarise the measurement properties of PROMs used for men with localised PCa according to the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) guidelines and to summarise feasibility aspects of the tools (eg, time to complete, fee payable, training required). Our findings should help physicians and researchers in selecting the most appropriate PROMs to use for HRQoL assessment in patients with localised PCa.

Evidence acquisition

The systematic review was conducted according to a predefined protocol based on the COSMIN methodology [7,8]. The review is reported in accordance with the PRISMA statement [9]. Several systematic reviews of HRQoL instruments in cancer patients adopted the COSMIN checklist to evaluate PROMs [10,11]. For this systematic review, instruments and measures for recording HRQoL as referred to as PROMs, which are typically defined as questionnaires used to assess every construct considered. The COSMIN approach defines the measurement properties important to PROMs: validity, responsiveness, and reliability. To evaluate these psychometric properties, the study was divided into four steps: identification, prioritisation, assessment, and summary of all PROMs considered. Four members of our research team (A.D., F.F., E.S.S., S.M.F.) undertook all stages of the process after the original electronic search, working independently of each other and then comparing outcomes at each stage

of the process. Any disagreements were resolved by discussion between the members of the research team.

Search strategy

First, to identify a comprehensive list of PROMs used in intervention effectiveness trials in localised PCa, we updated the systematic review by MacLennan et al [12] and identified the PROMs used in RCTs focused on patients with nonmetastatic PCa. We used the same inclusion and exclusion criteria as a pragmatic decision. Our aim was to select studies that are likely to influence clinical practice and we respected the hierarchy of evidence of the Oxford Centre for Evidence-Based Medicine guidelines [13] for RCTs. We extracted data on the core functional and QoL outcomes and domains: urinary function; bowel function; sexual function; and overall QoL. Studies including a mixed population of patients with localised or nonmetastatic locally advanced PCa were included. The PROMs identified are listed in Supplementary Table 1.

After identifying the eligible PROMs, a systematic review was performed to identify publications developing or evaluating psychometric properties of the identified PROMs in patients with localised PCa. The search evaluated studies published up to November 2019 without other time restrictions. The databases searched included MEDLINE (PubMed) and EMBASE using the PROM filter developed for PubMed by the Patient Reported Outcomes Measurement Group, University of Oxford, and a highly sensitive validated search filter for finding studies on measurement properties available on the COSMIN website [14,15]. Terms were agreed by the research team and limited to English-language articles that had developed, validated, or assessed the psychometric properties of the different PROMs [7].

Eligibility criteria

The inclusion criteria were as follows: (1) studies that assessed the measurement properties of a PROM (development and validation papers); (2) studies including patients with localised PCa (mixed populations were acceptable so long as data for patients with localised PCa were reported separately), with studies including participants with other disease types considered if the results for participants with localised PCa were reported separately; and (3) adequate evidence of content validity such as a qualitative study of the construct of interest in the target population.

The exclusion criteria were as follows: (1) studies assessing non–health-related PROMs (eg, treatment satisfaction); (2) studies in which the PROM was used exclusively to evaluate HRQoL in PCa patients and not reporting on psychometric properties; (3) studies including mainly patients with metastatic PCa or mixed populations with no separate reporting of data for patients with localised PCa; (4) meeting abstracts, conference abstracts, editorials, and commentaries; and (5) articles not in the English language.

To identify PROMs suitable for the assessment of psychometric properties, the team used search strings with specific keywords that are listed in the Supplementary material.

Screening

Abstracts and full texts were screened against the eligibility criteria by two reviewers independently between November 2019 and July 2020. Any disagreements were resolved by a third reviewer. Full-text papers were further explored independently by each of the four other reviewers to identify the final articles for inclusion in the review. The results from the database search and the study selection process are presented in Table 1.

Data extraction

Data were extracted for the following characteristics from each study: PROM(s) used, construct(s) measured, number of (sub)scales, number of items, description and version of the PROM, recall period, scoring information, time required to complete the PROM, information on population, training required for administration of the PROM, mode of administration, order form, type of license, number of published studies using the instrument, highest COSMIN rating, additional comments, and online example. This information was included in summary cards for each PROM (Supplementary Tables 2–8). The summary card format was based on the PROM assessment research of Turnbull et al in the critical care setting (www.improvelto.com/instruments/) [16].

Appraisal of methodological quality

To evaluate the methodological quality of studies, the COSMIN four-point checklist was used. The checklist criteria cover nine measurement properties, and the measurement

Table 1 – Overview of the patient-reported outcome measures (PROMs) extracted after screening of articles

PROM	Abstract screening	Full-text article screening	Full-text article extracted
International Consultation on Incontinence Questionnaire (ICIQ)	62	0	0
Expanded Prostate Cancer Index Composite (EPIC)	490	33	10
University of California-Los Angeles Prostate Cancer Index (UCLA-PCI)	167	16	4
EORTC Quality of Life Core 30 module (QLQ-C30)	177	10	3
EORTC Quality of Life Prostate Cancer 25 module (QLQ-PR25)	80	16	6
International Index of Erectile Function (IIEF)	443	17	2
Prostate Cancer Symptom Indices (PCSI)	451	1	0
Scandinavian Prostate Cancer Group study 4 (SPCG-4)	16	0	0
State-Trait Anxiety Inventory (STAI)	26	4	0
36-item Short-Form health survey (SF-36)	170	12	1
12-item Short-Form health survey (SF-12)	158	4	1
Total	2240	113	27

EORTC = European Organisation for Research and Treatment of Cancer.

properties of the studies included were assessed using the COSMIN risk-of-bias checklist. There are three domains covering various measurement properties: reliability (internal consistency, reliability, and measurement error), validity (content validity, structural validity, hypothesis testing, cross-cultural validity, and criterion validity), and responsiveness [7]. The Supplementary material lists the measurement properties and definitions [17].

Eligible studies were rated as very good, adequate, doubtful, inadequate, or not applicable for each measurement property [8]. The overall rating for the quality of each study for a measurement property was determined by the lowest rating for any standard: "the worst score counts" [16]. All results for the study measurement property of a PROM were quantitatively pooled or summarised against the criteria for good measurement properties to obtain the overall ratings.

Reporting of psychometric results

All PROMs were graded on the quality of the evidence. The internal consistency depends on the available evidence for structural validity because the prerequisite for interpretation of internal consistency is the unidimensionality. The quality of evidence for structural validity was the starting point for determining the quality of evidence for internal consistency. However, Cronbach's α is difficult to interpret as it is not based on a unidimensional scale [18]. Thus, the COSMIN manual for systematic reviews of PROMs recommends ignoring results of studies on the internal consistency of scales that are not unidimensional. The most important psychometric property is the content validity, which reflects whether the items of the PROM are relevant, comprehensive, and comprehensible to the construct of interest and the study population. This is why we considered this a vital property and used it as a threshold for inclusion: if a PROM could not demonstrate adequate content validity for the domain of interest (eg, urinary function) in our target population, it was not considered further. To evaluate the content validity, a subjective judgment by the reviewers is required on the adequacy of the initial qualitative work in the target population to identify constructs of importance. This should include the PROM development study, the quality and results of additional content validity studies on the PROMs (where available), and a subjective rating of the content of the PROMs [19].

Appraisal of levels of evidence

To determine the overall quality of each measurement property, a levels-of-evidence appraisal was undertaken. This process produced a final rating for each PROM for each measurement property. Using the Excel template provided by the COSMIN group, it was possible to evaluate the quality of the development of each PROM and to standardise the evaluation of the quality of the PROM design. Following this template, a rating system ranging from very good to inadequate was used. COSMIN checklist criteria were used to evaluate the quality of content validity studies regarding the comprehensiveness, comprehensibility, and relevance of each PROM item. To evaluate the content validity, the results from the single studies on PROMs development were rated. PROMs were then assigned to three categories to allow for an evidence-based recommendation: category A represents PROMs with evidence for sufficient content validity and at least low-quality evidence for sufficient internal consistency. PROMs rated as A can be recommended for use and the results can be trusted; PROMs rated as B have potential to be recommended but they require further research; PROMs rated as C have high-quality evidence for an insufficient measurement property.

All available studies were qualitatively summarised to determine whether overall, the relevance, comprehensiveness, comprehensibility, and overall content validity of the PROMs are sufficient, insufficient, or indeterminate. The overall ratings were accompanied by a grading for the quality of the evidence. Ratings for the levels of evidence are high (+), moderate (±), low (?), and very low (−). Levels of evidence criteria are presented in the Supplementary material.

Evidence synthesis

The most frequently used PROMs in RCTs of men with localised PCa were the International Index of Erectile Function (IIEF; n = 50), the Expanded Prostate Cancer Index Composite (EPIC; n = 26) and the International Consultation on Incontinence Questionnaire (ICIQ; n = 11). Supplementary Table 1 lists the PROMs identified in the systematic review and the corresponding publications. Some of the instruments used for assessment of QoL in PCa patients are not present among the PROMs suitable for psychometric evaluation. The reason for this resides in the rigorous methodology applied in our systematic review, whereby PROMs were considered only if they were adopted in RCTs focusing on patients with localised PCa. In addition, some studies evaluating additional PROMs were excluded because they did not meet the inclusion criteria in the full-text screening phase. The characteristics of the studies included are presented in Supplementary Table 2. After removal of duplicates and abstract screening, a total of 113 full texts were selected for further examination. Among those, 27 met the inclusion criteria and were evaluated according to the COSMIN checklist (Fig. 1). At the end of the screening phase we identified two generic PROMs: the 36-item Short-Form health survey (SF-36), the 12-item Short-Form health survey (SF-12); one cancer-generic PROM: the European Organisation for Research and Treatment of Cancer quality-of-life, 30-item core questionnaire (EORTC QLQ-C30) [20]; three PCa-specific PROMs: EPIC [21,22], the EORTC 25-item core questionnaire (QLQ-PR25), and the University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) [23]; and one specific PROM for erectile function: the IIEF [24]. The PCa-specific PROM (EPIC) was the most frequently evaluated in validation studies (n = 8), followed by the EORTC QLQ-C30 (n = 7) and the UCLA-PCI (n = 3). A summary of the number of items and concepts assessed for each of the PROMs evaluated is presented in Supplementary Table 2.

Table 2 presents COSMIN checklist scores for assessing the methodological quality of studies that reported COSMIN

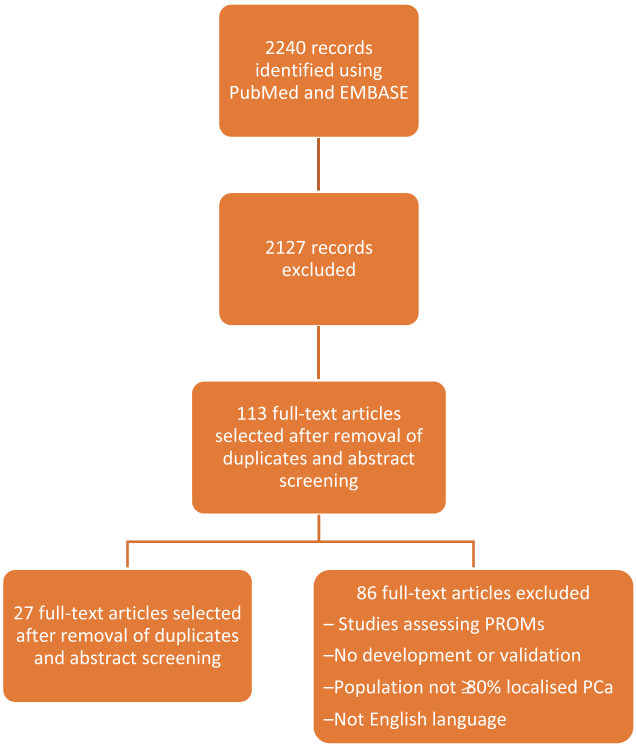

Fig. 1 – Flow diagram for study selection. PROMs = patient-reported outcome measures.

measurement properties for each PROM. Internal consistency was the most frequently reported property (21 studies). The reliability was calculated in 17 studies, the structural validity and hypothesis testing in nine, and the responsiveness and cross-cultural validity in seven. The least frequently reported property was measurement error (2 studies). The content validity was assessed for each study by the reviewers according to the COSMIN criteria. The best-performing properties were internal consistency and hypothesis testing, with eight of the 21 and five of the nine studies, respectively, receiving a score of very high. In addition, four of the 17 studies had very high reliability, and one of the seven studies had very high cross-cultural validity. The properties with the worst performance were content validity and structural validity, for which six of the 25 and three of the nine studies, respectively, scored very low. The internal consistency was presented as Cronbach's α, while the reliability was calculated using Pearson's or Spearman's correlation or, less frequently, the interclass correlation. Structural validity was assessed via either exploratory or confirmatory factor analysis.

In accordance with the COSMIN criteria, the PROMs were then categorised to recommend the most suitable PROMs for use in clinical practice and research settings. We categorised the UCLA-PCI and EORTC QLQ-PR25 as A (ie, can be recommended for use and results can be trusted), EPIC and EORTC QLQ-C30 as B (ie, have potential to be recommended but they require further research), and SF-12, IIEF, and SF-36 as C (ie, high-quality evidence for an insufficient measurement property). We scored the summarised content validity for each PROM, averaging across all the content validity scores previously assigned to each individual study.

According to the COSMIN methodology, greater importance is given to psychometric properties such as construct validity and internal consistency scores. Nevertheless, the other parameters remain equally important and desirable with all the instruments evaluated. Table 3 shows the summarised measurement properties for each PROM. UCLA-PCI showed moderate content validity and high internal consistency (summarised Cronbach's α 0.21–0.94); EORTC QLQ-PR25 had moderate content validity and moderate internal consistency (summarised Cronbach's α 0.39–0.87). Both EPIC and EORTC QLQ-C30 showed low content validity and high internal consistency (summarised Cronbach's α 0.46–0.96 and 0.68–0.94, respectively). Finally, SF-12, IIEF, and SF-36 had low content validity, while the internal consistency was not calculated in the studies on SF-12 and IIEF and was scored as moderate in the study on SF-36 (summarised Cronbach's α 0.77–0.93). An overview of each PROM, along with feasibility characteristics such as time to complete, licensing requirements, and administrator training [25], is presented in Supplementary Tables 4–10. The concept of feasibility is related to the concept of clinical utility, but feasibility focuses on PROMs whereas clinical utility refers to an intervention [26]. Interpretability and feasibility are not measurement properties because they do not refer to the quality of a PROM. However, they are considered important aspects for well-considered selection of a PROM. As observed in Supplementary Table 3, most of the instruments have free access and are easily available, apart from EORTC QLQ-C30 and EORTC QLQ-PR25, which need a user agreement to obtain permission to use them. They all take a few minutes to fill in and no specific training is needed before they are adopted. UCLA-PCI is categorised as A, which means that in addition to the statistically significant features, it has good feasibility (ie, it takes little time, requires no specific training for administration, does not require access costs, and is a specific tool for measuring QoL in the setting of PCa). However, UCLA-PCI does not directly assess hormonal symptoms, whereas EORTC QLQ-PR25 does, and therefore the EORTC QLQ-PR25 module is the most appropriate for use in the population with localised PCa together with the EORTC QLQ-C30 to assess HRQoL for generic cancer patients.

Discussion

Our study rigorously applied the COSMIN methodology to assess the psychometric properties of PROMs to be used in research studies and, ideally, in clinical practice for patients with localised PCa in the context of a wider COS development project that included patients, health care professionals, and industry partners. The psychometric properties of all the PROMs selected were assessed using a rigorous and standardised tool after performing a systematic review of the literature. Overall, 27 studies that reported on psychometric properties of PROMs met the inclusion criteria. Although none of them met all the COSMIN standards for methodological quality, the "best fit" method was adopted to make our assessment objective. This represents the first attempt to systematically assess

Table 2 – COSMIN risk-of-bias checklist scores for the methodological quality of each study by measurement property and patient-reported outcome measure (PROM)

PROM[a]	Study[b]	Content validity	Structural validity	Internal consistency	Reliability	Measurement error	Hypothesis testing	Responsiveness	Cross-cultural validity
UCLA-PCI	Litwin et al, 1998 [23]	Very good	Adequate	Very good	Adequate	–	Very good	–	Very good
	Kakehi et al, 2002 [34]	Adequate	–	Adequate	Adequate	–	–	–	–
	Korfage et al, 2003 [35]	Adequate	–	–	Very good	–	–	Very good	–
	Gacci et al, 2005 [36]	Adequate	–	Very good	Very good	–	–	–	–
SF-36	Van Leeuwen et al, 2017 [37]	Adequate	–	Adequate	–	–	–	–	Adequate
SF-12	Choi et al, 2016 [38]	Adequate	–	–	–	–	–	Doubtful	–
EORTC QLQ-PR25	Van Andel et al, 2008 [39]	Adequate	–	Very good	–	–	–	Adequate	–
	Arraras et al, 2009 [40]	Adequate	–	–	Adequate	–	Very good	–	Very good
	Chang et al, 2012 [41]	Adequate	–	Doubtful	–	–	–	–	–
	Park et al, 2013 [42]	Adequate	Adequate	Doubtful	–	–	–	Adequate	Adequate
	Chu et al, 2014 [43]	Inadequate	–	Adequate	–	–	–	Adequate	–
	O'Leary et al, 2015 [44]	Adequate	Adequate	–	Adequate	–	–	–	–
EORTC QLQ-C30	Curran et al, 1997 [45]	Inadequate	Inadequate	Adequate	Adequate	–	–	–	Very good
	Bestmann et al, 2006 [46]	Adequate	Adequate	Very good	Very good	–	Very good	–	–
IIEF	Karakiewicz et al, 2005 [47]	Doubtful	–	–	Doubtful	–	–	–	–
	Lin et al, 2016 [48]	Adequate	–	–	Adequate	–	–	–	–
EPIC	Kakehi et al, 2007 [49]	Low	Inadequate	Very good	Very good	–	Adequate	–	–
	Chung et al, 2010 [50]	Inadequate	–	Very good	Very good	–	–	–	–
	Chang et al, 2011 [51]	Inadequate	–	Very good	–	–	–	–	–
	Alves et al, 2013 [52]	Inadequate	–	Very good	–	–	Very good	–	–
	Schmidt et al, 2014 [29]	Adequate	–	Inadequate	Inadequate	–	–	Adequate	–
	Anota et al, 2016 [53]	Adequate	Inadequate	Very good	Very good	–	Very good	–	Inadequate
	Axcrona et al, 2017 [54]	Doubtful	Adequate	Adequate	–	–	–	–	–
	Umbehr et al, 2018 [55]	Adequate	Doubtful	Very good	Adequate	Doubtful	Very good	Inadequate	–
	Lee et al, 2018 [56]	Adequate	–	Adequate	Adequate	–	Doubtful	–	–
	Einstein et al, 2019 [57]	Doubtful	–	Adequate	–	–	–	–	Very good
	Marzorati et al, 2019 [58]	Doubtful	–	Very good	Adequate	Adequate	Very good	–	–

[a] The full names of the PROMs are given in Table 1.
[b] Further study details are provided in Supplementary Table 2.

Table 3 – Summarised measurement properties for each patient-reported outcome measure (PROM)

PROM (category) [a]	Structural validity	Internal consistency	Cross-cultural validity	Reliability	Measurement error	Hypothesis testing	Responsiveness
UCLA-PCI (A)	Moderate (between-factor correlation 0.31–0.39)	High (summarised Cronbach's α 0.21–0.94)	Moderate (similar samples)	Moderate (summarised ICC/PMC 0.03–1.00)	–	–	–
EORTC QLQ-PR25 (A)	Moderate (summarised RMSEA 0.044, SRMR 0.036, CFI 0.95)	Moderate (summarised Cronbach's α 0.39–0.87)	Moderate (similar samples)	Moderate (summarised Cronbach's α 0.40–0.86)	–	–	–
EPIC (B)	Low (multifactor, 13 factors)	High (summarised Cronbach's α 0.46–0.96)	–	Moderate (summarised ICC 0.088–0.804)	Moderate (summarised SEM 3.9–7.1, RMSEA 0.44–0.57)	Low (>10 hypotheses)	Low (summarised responsiveness 88.9, SRM 4–12)
EORTC QLQ-C30 (B)	Low (multifactor, 9 factors)	High (summarised Cronbach's α 0.68–0.94)	Low (not similar samples)	Moderate (summarised Cronbach's α 0.58–0.89)	–	High (2 hypotheses)	–
SF-12 (C)	–	–	–	–	–	–	–
IIEF (C)	–	–	–	Moderate (summarised ICC 0.37–0.83)	–	–	–
SF-36 (C)	–	Moderate (summarised Cronbach's α 0.77–0.93)	Moderate (similar samples)	–	–	–	–

CFI = comparative fit index; ICC = interclass correlation; PMC = product-moment correlation; RMSEA = root mean square error of approximation; SEM = ; SRM = ; SRMR = standardised root mean square residual.
[a] The full names of the PROMs are given in Table 1. Category A: can be recommended for use and the results can be trusted. Category B: has potential to be recommended but requires further research. Category C: has high-quality evidence for an insufficient measurement property.

PROMs for use in clinically localised PCa using a validated rigorous approach.

Our study yielded several results. First, although our systematic review identified 12 PROMs used in RCTs on localised PCa, studies assessing the psychometric properties were not available for five of these. For example, the ICIQ and International Prostate Symptom Score are commonly used in localised PCa and were adopted in 11 and seven RCTs, respectively. However, no data are available regarding their psychometric properties. Although both these questionnaires are considered as reliable PCa-specific tools by clinicians and typically used in retrospective studies and prospective trials, our observations highlight that evidence-based recommendations are urgently needed to support the PROM that clinicians and researchers should use to evaluate patients with localised disease. This will have a relevant impact on assessing the external validity of ongoing trials, comparing results among different studies evaluating patient-reported outcomes, and directly addressing the challenges of heterogeneity in outcome reporting. Finally, our observations highlight the need for more research activities aimed at validating the psychometric properties of available PROMs assessing cancer-specific domains such as urinary incontinence and erectile function.

Second, seven of the 11 PROMs identified had only limited data available regarding their psychometric properties. Among those, SF-36 and SF-12 provide information about patient HRQoL in general, but not specifically about the core domains of urinary, bowel, and sexual function. The SF-36, SF-12, and IIEF instruments are accepted as being valid, reliable, and sensitive for a wide range of health problems [24,27]. The IIEF covers sexual function but not urinary or bowel function. However, the SF-12, SF-36, and IIEF may lack sensitivity in measuring PCa-specific issues. They have high-quality evidence for an insufficient measurement property and we cannot recommend these tools for use in routine practice or research. By contrast, the EORTC QLQ-C30 and EPIC have been scored as good tools for assessing QoL in PCa patients, but they showed low content validity and high internal consistency. Therefore, they have potential to be recommended but they require further research. Of note, adoption of the EPIC instrument has been recommended by the International Consortium for Health Outcomes Measurements (ICHOM). However, further studies are needed before its use can be routinely recommended in the ideal scenario. The EORTC QLQ-C30 scores are an adequate reflection of the dimensionality of the construct to be measured with adequate interrelatedness among the items. Moreover, the performance of the items on translated or culturally adapted EORTC QLQ-C30 versions are an adequate reflection of the performance of the items of the original version of the PROM, and the total variance in the measurements of this PROM is due to "true" differences between patients. Even though it was categorised as B overall, EORTC QLQ-C30 had the highest quality of evidence available for assessing HRQoL in patients with localised PCa and therefore we recommend it for assessing this domain.

Both the EORTC QLQ-PR25 and UCLA-PCI instruments performed well and have the most positive COSMIN ratings. Therefore, we classified these as A, since the first shows

moderate content validity and high internal consistency, and the second shows moderate content validity and moderate internal consistency [28]. EORTC QLQ-PR25 reflects mostly the performance of the items for PCa QoL. UCLA-PCI might have a good internal structure (structural validity, internal consistency, cross-cultural validity) because it refers to how the different items in the PROM are related, which is important to help understand how items might be combined into a scale or subscale. This PROM specifically exhibits good compatibility for evaluating HRQoL in PCa patients in routine clinical practice. However, UCLA-PCI does not directly assess hormonal symptoms, whereas EORTC QLQ-PR25 does. Therefore, considering that hormonal symptoms are one of the core outcomes, we recommend the EORTC QLQ-PR25 module as the most appropriate for use in localised PCa [6]. Of note, this module should be used in conjunction with the EORTC QLQ-C30 general module, which assesses patients' physical, psychological, and social functions.

As highlighted in the summary cards, beyond the psychometric properties there are feasibility aspects that should be considered. These relate, for example, to the availability of the PROMs and their costs, as well resources required, such as staff training and time to complete the instrument. These resources may differ between the research and routine practice settings. Considering the psychometric and feasibility information together, the PIONEER Consortium recommends that EORTC QLQ-30 and the QLQ-PR25 module should be used in both research and routine care settings. Previous studies recommended different PROMs for implementation in clinical practice (EPIC, Patient-Oriented Prostate Utility Scale, and Prostate Cancer-Quality of Life) [29]. However, the evidence behind these recommendations is based on historic cohorts and considered only PCa patients with early-stage disease. By contrast, our systematic review considered contemporary instruments developed up to 2014 and applied a standardised systematic approach using the COSMIN methodology to identify the strongest questionnaires at the psychometric level.

Taken together, the recommended PROMs provide the most coverage of the HRQoL and functional domains of the COS while being the soundest measures available of the core outcome domains in localised PCa. These tools should be administered at baseline and at different time points during follow-up according to the type of treatment delivered, as recommended by ICHOM. Researchers and clinicians should be encouraged to use the EORTC QLQ-30 and QLQ-PR25 instruments. Use of the same tools to measure the main domains for results ensures less heterogeneity in the evidence base. The use of common outcome measurement instruments will facilitate interpretation of the evidence across different RCTs and evidence summaries in meta-analyses, with a consequent impact on formulating recommendations for clinical guidelines. Furthermore, use of the same measures in routine clinical practice and other real-world data sources for evidence will facilitate integration and analysis in big data platforms such as PIONEER. This has powerful implications for benchmarking via audit and feedback from both value-driven [30] and quality improvement perspectives [31]. Beside disease-specific validated tools, generic measures are useful for comparability because of their greater practicality and may be relevant to the multiple stakeholders involved in PCa management. For example, policy-makers may look to generic instruments (and quality-adjusted life years) to ascertain whether to fund one therapy, not just against other potential PCa interventions but also in comparison to interventions in other settings to ensure that cost-effective care is delivered to maximise health outcomes. In this light, further research is needed in this setting to validate generic PROMs for patients with localised PCa that should be considered in addition to disease-specific tools.

Although our initial protocol also included a Delphi survey after assessment of the PROMs using the COSMIN criteria for localised PCa, the identification of only two PROMs graded as A (EORTC QLQ-PR25 and UCLA-PCI) limited the potential value of a formal Delphi survey. Indeed, it is likely that physicians would indicate as appropriate the use of most of the PROMs adopted rather than the ones with a more solid construct and validity. However, our work should inform physicians regarding the availability of validated PROMs assessed via a systematic approach in the setting of localised PCa regardless of their preferences. The recommendation to use these validated tools would not necessarily translate into their adoption by clinicians in everyday practice and therefore implementation measures might be necessary. While the implementation of PROMs in standard care is still in development [32], useful guidance is already available for reporting, analyses, and translations of PROMs. For instance, the EORTC has developed a manual for the use of their measures in daily clinical practice [33].

Some potential limitations of our study should be discussed. First, our systematic review was restricted to the English language, which may have introduced a language bias. At the same time, our aim was to compare the psychometric aspects of HRQoL instruments, and there is no evidence to suggest that this objective was influenced by the language restriction. One of the main strengths of this study is that we have been able to categorise the PROMs in the A, B, and C categories according to the different psychometric properties assessed. In addition, use of the COSMIN checklist is a strength as it allows the content validity of PROMs to be calculated in a standardised manner through quality scores for measurement properties on the basis of systematic reviews. This should guide physicians in decisions regarding which PROMs should be adopted in their clinical practice regardless of their subjective preferences.

Conclusions

The psychometric properties of several PROMs that are currently used for patients with localised PCa have been poorly assessed so far. Although UCLA-PCI was characterised by moderate content validity and high internal consistency, it does not directly assess hormonal symptoms, while the EORTC QLQ-PR25 does. Since EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25

module. Therefore, the PIONEER Consortium recommends that EORTC QLQ-30 and QLQ-PR25 should be used in both research and routine care settings to measure the core domains of urinary, bowel, and sexual function, hormonal symptoms, and HRQoL.

Author contributions: Giorgio Gandaglia 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.

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Obtaining funding: Van Hemelrijck, N'Dow, Briganti.
Administrative, technical, or material support: None.
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Other: None.

Financial disclosures: Giorgio Gandaglia certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Olalekan Lee Aiyegbusi reports funding from the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, the NIHR Applied Research Centre at the University of Birmingham and University Hospitals Birmingham NHS Foundation, Innovate UK (part of UK Research and Innovation), Gilead Sciences, and Janssen Pharmaceuticals, and personal fees from Gilead Sciences, GlaxoSmithKline, and Merck outside the submitted work. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: PIONEER is funded through the IMI2 Joint Undertaking and is listed under grant agreement number 777492. This joint undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. Paula R. Williamson is a National Institute for Health Research (NIHR) Senior Investigator (award number NF-SI_0513-10025 supporting this work). The views expressed in this article are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Acknowledgements: We would like to thank Caroline Terwee and Sanna Prinsen from the COSMIN initiative for their advice on our study design and application of the COSMIN tools.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2021.10.004.

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