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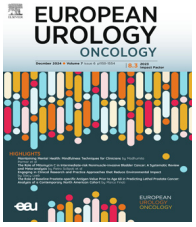

European Association of Urology

Review

Patient-reported Outcome Measures and Experience Measures After Active Surveillance Versus Radiation Therapy Versus Radical Prostatectomy for Prostate Cancer: A Systematic Review of Prospective Comparative Studies

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Abstract

Background and objective: Current management options for localized prostate cancer (PCa) include radical prostatectomy (RP), radiotherapy (RT), and active surveillance (AS). Despite comparable oncological outcomes, there is still lack of evidence on their comparative effectiveness in terms of patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs). We conducted a systematic review of studies comparing PROMs and PREMs after all recommended management options for localized PCa (RP, RT, AS).

Methods: A literature search was performed in the MEDLINE, EMBASE, and Cochrane CENTRAL databases in accordance with recommendations from the European Association of Urology Guidelines Office and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. All prospective clinical trials reporting PROMs and/or PREMs for comparisons of RP versus RT versus AS were included. A narrative synthesis was used to summarize the review findings. No quantitative synthesis was performed because of the heterogeneity and limitations of the studies available.

Key findings and limitations: Our findings reveal that RP mostly affects urinary continence and sexual function, with better results for voiding symptoms in comparison to other treatments. RT was associated with greater impairment of bowel function and voiding symptoms. None of the treatments had a significant impact on mental or

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Active surveillance

physical quality of life. Only a few studies reported PREMs, with a high rate of decision regret for all modalities (up to 23%).

Conclusions and clinical implications: All recommended treatments for localized PCa have an impact on PROMs and PREMs, but for different domains and with differing severity. We found significant heterogeneity in PROM collection, so standardization in real-world practice and clinical trials is warranted. Only a few studies have reported PREMs, highlighting an unmet need that should be explored in future studies.

Patient summary: We reviewed differences in patient reports of their outcomes and experiences after surgical prostate removal, radiotherapy, or active surveillance for prostate cancer. We found differences in the effects on urinary, bowel, and sexual functions among the treatments, but no difference for mental or physical quality of life. Our results can help doctors and prostate cancer patients in shared decision-making.

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1. Introduction

According to international guidelines, management options for localized prostate cancer (PCa) include radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy (BT), and active surveillance (AS) [1,2]. As these strategies have comparable PCa-specific and overall mortality rates [3,4], selection of the best management option for clinically localized PCa is often based on the clinician's and patient's view of the trade-off between treatment-specific risks, benefits, and side effects. All PCa treatments are associated with specific side effects that may evolve or resolve over time and potentially impair patient quality of life (QoL) [5–8]. Moreover, as baseline function is a strong predictor of post-treatment functional outcomes [8], the clinician should also evaluate the patient's baseline urinary, bowel, and sexual function to choose the best tailored treatment after shared decision-making [2].

Patient-reported outcome measures (PROMs) are standardized, validated questionnaires that are completed by patients in the peritreatment period that allow a comparison of outcomes before and after a procedure and measurement of the efficacy of a clinical intervention from the patient's perspective [9]. PROMs also measure a patient's perception of their health in relation to a specific disease [10].

Similarly, patient-reported experience measures (PREMs) provide objective information on a patient's view of their experience while receiving care, including organizational features (eg, information provided by health care professionals), feelings (eg, attention to pain), and other aspects of their care (eg, waiting time during appointments). PREM results are indicators of the quality of care and provide an insight into patient expectations, which is useful for the redesign of health care pathways to meet these expectation [11,12].

Integration of PROMs and PREMs in preoperative shared decision-making is an unmet clinical need. Choosing the correct validated tool to measure PROMs or PREMs for a specific patient cohort is crucial [11]. However, a lack of standardization on how PROMs/PREMs are collected, analyzed, and interpreted remains, hampering their ability to inform benefit-risk assessments of different PCa treatments [13,14].

To fill this gap, we conducted a systematic review to report and compare PROMs and PREMs from patients treated with one of the options for localized PCa, and to provide a contemporary view of which PROMs and PREMs are currently used in studies for men with localized PCa.

2. Methods

2.1. Literature search

We performed a systematic review in accordance with recommendations from the European Association of Urology (EAU) Guidelines Office [15] and the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16] (Supplementary Table 1). The protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42023485528).

The literature search was performed on July 7, 2023 in the MEDLINE, EMBASE, and Cochrane CENTRAL (via Ovid) databases. Terms related to localized PCa, interventions, and PROMs/PREMs were searched using Boolean operators. The complete search strategy is provided in the Supplementary material.

2.2. Research question

The PICOS (Patient, Intervention, Comparison, Outcome, Study type) framework was used to frame and answer the clinical question:

- P: Adult (>18 yr) male patients with localized PCa who had not undergone any previous treatment before their primary treatment for PCa.
- I: Active management for PCa according to EAU guideline recommendations. In particular, management options included: AS, RP (any approach), or RT (including EBRT and low-dose-rate or high-dose-rate BT, with or without neoadjuvant, concurrent, or adjuvant androgen deprivation therapy (ADT).
- C: Comparison of RP versus RT (EBRT or BT) versus AS; all three management options had to be included in the study.

- O: PROMs and/or PREMs on urinary function and continence, bowel and sexual function, and QoL.
- S: Prospective randomized and nonrandomized studies.

2.3. Study screening and selection

Studies were included according to the PICOS eligibility criteria. Reviews, letters to the editor, case reports, meeting

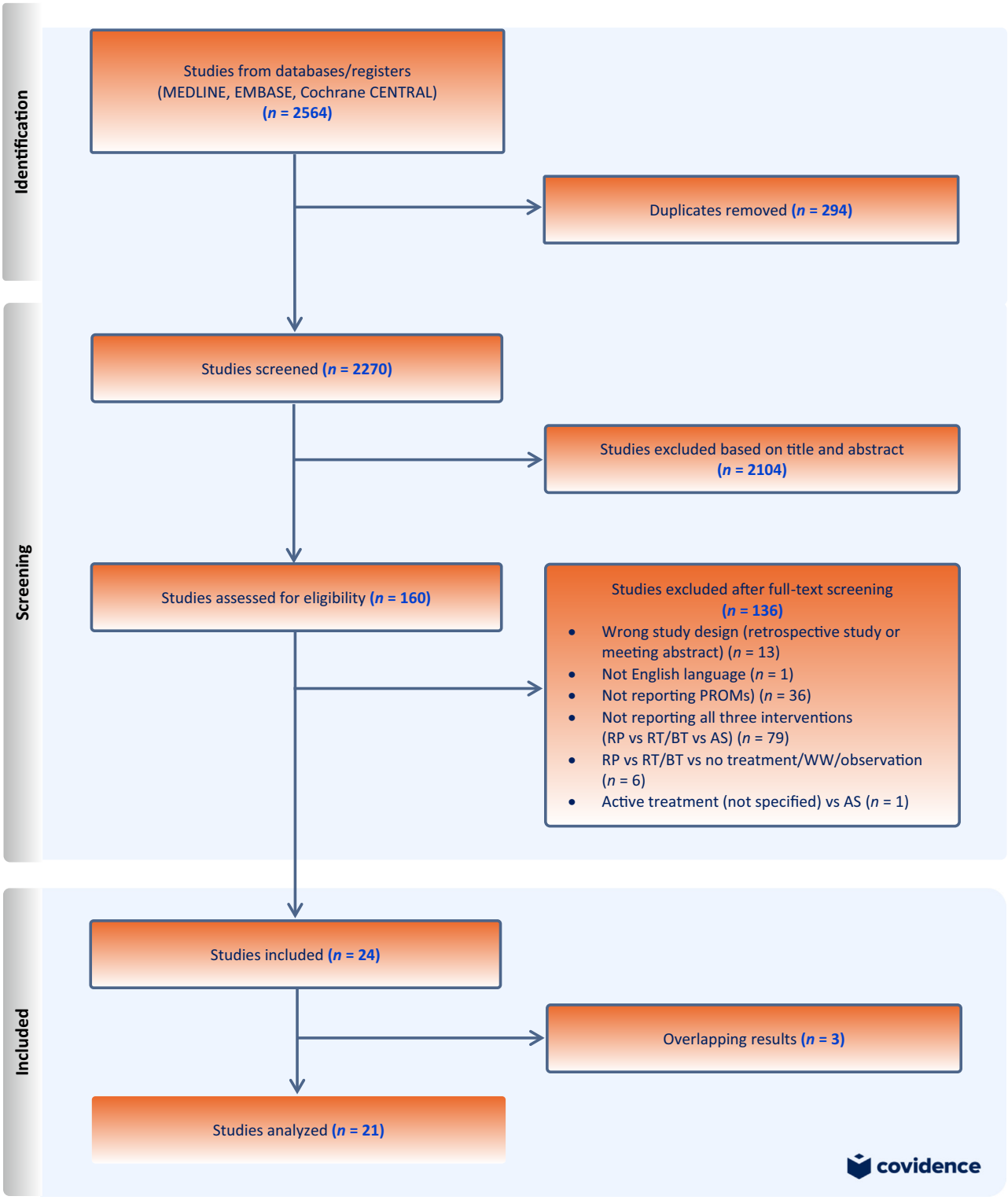

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. AS = active surveillance; PROM = patient-reported outcome measure; RP radical prostatectomy; RT = radiation therapy; WW = watchful waiting.

abstracts, and retrospective studies were excluded. Only papers in English were eligible for inclusion.

All reports retrieved were independently screened by two authors each (A.A., R.N., P.M., D.C., E.D., and G.R.R.) using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). A third author resolved discrepancies via discussion. The full text of the screened papers was selected if it was found pertinent to the aim of the review.

Only prospective comparative studies reporting validated PROMs/PREMs for all three interventions (RP, RT, and AS) were included to minimize selection bias and confounding and to facilitate interpretation of the data. Studies reporting within-treatment comparisons only (eg, RT vs RT + ADT) were excluded. Studies on AS were included only if there was a prespecified protocol. For studies with multiple publications reporting PROMs/PREMs from the same trial, only papers with the most up-to-date data or with complete data for each outcome were included.

2.4. Data extraction and analysis

An Excel data extraction form developed a priori was used to collect information on study design, participant demographics, characteristics of interventions, and outcome measures. Six authors (A.A., R.N., P.M., E.D., G.R.R., and M. M.) extracted data for the prespecified outcomes. Descriptive statistics were used to summarize baseline characteristics. For studies with other intervention groups besides RP, RT, and AS, only the data relevant to the review were selected.

Two authors (A.A. and P.M) independently evaluated the study quality and assessed the risk of bias. Discrepancies were resolved via discussion. The Cochrane risk-of-bias tool was used for randomized controlled trials (RCTs) [17] (Supplementary Figure 1). The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used for prospective studies [18] (Supplementary Fig. 2). Possible confounders were considered according to consensus among the authors from the literature review.

Given the quality of the evidence retrieved, a quantitative synthesis or meta-analysis of findings from the studies was not feasible. Therefore, a narrative synthesis was used to summarize the review findings.

3. Results

3.1. Literature search and characteristics of the studies included in the review

The literature search identified 2564 papers. After removal of duplicates and screening by title and abstract, 160 full-text papers were screened for appropriateness. Of the five papers reporting data from the ProtecT RCT [19–23], only two were included as they reported the most complete PROMs data [19,20]. Two cross-sectional studies by Venderbos et al [24,25] were judged to be overlapping series, so only the less recent one was included as it contained a greater amount of PROM/PREM data [24]. As a result, 21 papers were included for analysis of the results [7,8,19,20,24,26–41]. Figure 1 shows a PRISMA flow diagram of the study selection process.

Among the 21 papers included in the review, one reported data from an RCT (ProtecT trial) [19], 12 were prospective nonrandomized longitudinal studies [7,8,20,26–33,41], three were population-based prospective studies [34–36], and five were cross-sectional studies [24,37–40]. Table 1 provides an overview of the questionnaires used to assess the PROMs reported in the studies. A complete list of the studies included and their characteristics is provided in Table 2. PREMs assessed in the studies are summarized in Table 3. A comprehensive overview of the PROMs on urinary, sexual and bowel function is provided in Supplementary Tables 2–4.

The complete narrative evidence synthesis for each PROM domain analyzed in the review is presented in the Supplementary material.

3.2. PROMs after AS versus RT versus RP

3.2.1. PROMs for urinary function

Sixteen studies included in the review reported outcomes for urinary function. Of these, two were RCTs, 11 were prospective studies, and three were observational studies. Twelve papers reported data on urinary function using the Expanded Prostate Cancer Index Composite (EPIC-26) instrument, while the remaining four used the European Organisation for Research and Treatment of Cancer-Quality-of-Life Questionnaire prostate cancer module (EORTC-QLQ-PR25), the Prostate Cancer Symptom Indices (PCSI) urinary obstructive and irritative domains, the International Prostate Symptom Score (IPSS), or the University of California-Los Angeles Prostate Cancer Index (UCLA-PCI).

As reported for several studies, obstructive symptoms usually improve after RP, while up to 30–60% of patients treated with RT (mostly in the case of BT) report acute voiding and storage symptoms, with resolution over a period of 1–2 yr to a level similar to baseline [41,42].

A discrepancy was noted in some studies reporting worse declines in urinary function after surgery than after other treatments [43–45]. However, this variation could be explained by the use of different PROMs, as the UCLA-PCI tool primarily focuses on urinary incontinence, while studies reporting less storage/voiding symptoms mainly used the EPIC tool, which addresses symptoms that provide a more comprehensive assessment of urinary QoL [46].

3.2.2. PROMs for urinary incontinence

Fourteen studies reported PROMs on urinary incontinence (UI), using EPIC-26 (n = 11), the International Consultation on Incontinence Questionnaire or International Continence Society Male Short Form (n = 3), EORTC QLQ-PR25 (n = 1), or PCSI (n = 1).

Unlike storage and voiding symptoms, which are frequent before treatment, UI is quite uncommon (<5% of patients used pads at baseline [42,47,48]). At 2 mo after surgery, up to 60–70% of patients reported use of pads, with a decrease to 20% by 2 yr [42,49]. Conversely, the rate of pad use after EBRT and BT was stable during follow-up, with ~5% of patients reporting UI requiring pad use at 2 yr [42,47].

Table 1 – Overview of the questionnaires used to assess patient-reported outcome measures

Measure	Items	Domains	Score range
Expanded Prostate Cancer Index Composite (**EPIC**)	50	• Urinary incontinence (4 items), irritation/obstruction (7 items), overall urinary function (1 item) • Sexual function (9 items) and bother (4 items) • Bowel function (7 items) and bother (7 items) • Hormonal function (5 items) and bother (6 items)	0–100 Higher scores = less symptoms/bother
Expanded Prostate Cancer Index Composite-26 items (**EPIC-26**)	26	• Urinary incontinence (4 items), irritation/obstruction (4 items), overall urinary function (1 item) • Bowel function (6 items) • Sexual function (6 items) • Vitality/hormonal function (5 items)	0–100 Higher scores = less symptoms/bother
EORTC Quality of Life Questionnaire -Core 30 score (**EORTC QLQ-C30**)	30	• Functional scales: physical (5 items), role (2 items), social (2 items), emotional (4 items) and cognitive (2 items) functioning • Symptoms scales: dyspnea (1 item), pain (2 item), fatigue (3 item), insomnia (1 item), loss of appetite (1 item), nausea and vomiting (2 items), constipation (1 item), diarrhea (1 item), perceived financial impact (1 item) • Global health status/QoL (2 items)	0–100 Higher scores = higher level of functioning/ QoL for functional scales and QoL, or greater bother for symptoms
EORTC Quality of Life Questionnaire-Prostate Cancer 25 (**EORTC QLQ-PR25**)	25	• Urinary symptoms (8 items) and incontinence (1 item) • Bowel symptoms (4 items) • Hormonal symptoms (6 items) • Sexual function (6 items)	0–100 Higher scores = greater function (sexual function) or more symptoms/bother (other domains)]
Memorial Anxiety Scale for Prostate Cancer (**MAX-PC**)	18	• Prostate cancer anxiety (11 items) • PSA anxiety (3 items) • Fear of reoccurrence (4 items)	0–54 Higher scores = greater anxiety (score >27 = clinically anxious)
International Continence Society male Short Form (**ICSmale-SF**)	11	• Voiding symptoms (5 items) • Urinary incontinence (6 items)	0–20 (voiding symptoms) 0–24 (incontinence) Higher scores = greater symptoms/bother
ICIQ Urinary Incontinence Short Form (**ICIQ-UI-SF**)	4	• Urinary incontinence (4 items)	0–21 Higher scores = greater symptoms/bother
36-item Short-Form Survey (**SF-36**)	36	• General health perceptions/QoL (6 items) • Limitations in physical activities (10 items) • Limitations in social/role activities (9 items) • Pain (2 items) • Emotional well-being (7 items) • Vitality (energy and fatigue) (2 items)	0–100 Higher scores = better health/functioning
12-item Short-Form Survey (**SF-12**)	12	• General health perceptions/QoL (1 item) • Limitations in physical activities (2 items) • Limitations in social/role activities and pain (6 items) • Emotional wellbeing (2 items) • Vitality (energy and fatigue) (1 item)	0–100 Higher scores = less symptoms/bother
15-Dimensions questionnaire (**15D**)	15	Single items: breathing; mental function; communication; vision; mobility; usual activities; vitality; hearing; eating; elimination; sleeping; distress; symptoms; sexual activity; depression	0–1 0 = dead; 1 = no problems for any dimension
Hospital Anxiety and Depression Scale (**HADS**)	14	• Anxiety (7 items) • Depression (7 items)	0–21 Higher scores = greater anxiety/depression
Prostate Cancer Symptom Indices (**PCSI**)	31	• UI severity (3 items) and bother (1 item) • Obstruction severity (5 items) and bother (5 items) • Bowel problems (6 items) and bother (4 items) • Sexual dysfunction (5 items) and problems (2 items)	0-100 [higher scores = greater symptoms/bothers]
Short form of the WHO Quality of Life Questionnaire (**WHOQOL-BREF**)	26	• Overall QoL/general health (1 item) • Physical health (8 items) • Psychological health (6 items) • Social relationships (3 items) • Environmental QoL (8 items)	4–20 Higher scores = higher level of health/QoL
CES Depression Scale, 10-item version (**CES-D-10**)	10	• Emotional wellbeing/depression (10 items)	0–30 Higher scores = greater depression (score >10 = depression)
UCLA Prostate Cancer Index (**UCLA-PCI**)	20	• Urinary function (5 items) and bother (1 item) • Sexual function (8 items) and bother (1 item) • Bowel function (4 items) and bother (1 item)	0–100 Higher scores = less symptoms/bother
EuroQol-5 Dimension-5 Level (**EQ-5D-5L**): EuroQol-Descriptive system (**EQ-5D**) + EuroQol-Visual Analog Scale (**EQ-VAS**)	5	• Mobility (1 item) • Self-care (1 item) • Usual activities (1 item) • Pain/discomfort (1 item) • Anxiety/depression (1 item)	0–100 0 = worst health 100 = best health
State-Trait Anxiety Inventory (**STAI**)	40	• Emotional well-being/anxiety	20–80 Higher scores = greater anxiety

CES = Center of Epidemiologic Studies; EORTC = European Organization for Research and Treatment of Cancer; ICIQ = International Consultation on Incontinence Questionnaire; PSA = prostate-specific antigen; QoL = quality of life; UCLA = University of California-Los Angeles; UI = urinary incontinence; WHO = World Health Organization.

Table 2 – General characteristics of the studies included in the review

Study	Design	Pts	Interventions, *n* (%)	FU (mo)	Age (yr) [b]	pPSA (ng/ml) [c]	GS, *n* (%)	Risk group, *n* (%)
Donovan 2016 [19]	RCT	1643	RP: 553 (33.6) RT: 545 (33.2) AS: 545 (33.2)	72	62 (5)	RP: 4.9 (3.7–6.7) EBRT: 4.8 (3.7–6.7) AS: 4.7 (3.7–6.7)	6: 1266 (77) 7: 339 (20.6) ≥8: 37 (2.2)	NR
Lane 2022 [20]	RCT	2565	RP: 750 (29.2) EBRT: 603 (23.5) BT: 77 (3.0) AS: 1135 (44.2)	72	62 (50–73)	NR	NR	NR
Ernstmann 2012 [26]	PLS	1216	RP: 702 (57.4) RT: 142 (11.6) AS: 154 (12)	6	68 (44–84)	NR	NR	NR
Barocas 2017 [7]	PLS	2550	RP: 1523 (59.7) RT: 598 (23.5) AS: 429 (16.8)	36	63.8 (63.5–64.1)	<4: 529 (21%) 4–10: 1680 (66%) 10–20: 257 (10%) ≥20: 84 (3%)	6: 1324 (52) 3+4: 703 (28) 4+3: 263 (10) ≥8: 252 (10)	LR: 1144 (45) IR: 983 (39) HR: 417 (16)
Chien 2017 [27]	PLS	5727	ORP: 199 (3.5) RARP: 1861 (32.5) EBRT: 309 (5.4) BT: 132 (2.3) AS: 2389 (41.7) Other: 837 (14.3)	24	64.3 (8.5)	11.6 (17.3)	6: 3215 (56.6) 7: 1715 (30.2) ≥8: 748 (12.5)	NR
Sciarra 2018 [41]	PLS	220	RP: 99 (45) RT: 102 (46.4) AS: 19 (8.6)	12	RP 66 (48–77) RT 70 (65–78) AS 70 (66–78)	RP: 7.7 (3.7) RT: 14.0 (4.9) AS: 5.2 (0.8)	6: 70 (31.8) 3+4: 88 (40.0) 4+3: 58 (26.4) ≥8: 4 (1.8)	NR
Hoffman 2020 [8]	PLS	2005	RP: 1077 (53.7) EBRT: 261 (13) EBRT+ADT: 217 (10.8) LDR-BT 87 (4.3) AS: 363 (18.1)	60	65 (58–71)	5.5 (5–10)	6: 1052 (52.5) 3+4: 450 (22.4) 4+3: 255 (12.7) ≥8: 247 (12.3)	LR: 918 (45.8) IR: 687 (34.3) HR: 400 (20)
Nguyen-Nielsen 2020 [28]	PLS	15465	RP: 3843 (28.2) RT±ADT: 2348 (17.2) AS: 2514 (18.4) Other: 4937 (36.2)	36	69 (64–74)	11.8 (7.0–29.0)	6: 4092 (28.3) 7: 6163 (42.6) ≥8: 4204 (29.1)	NR
van Stam 2020 [29]	PLS	434	RP: 195 (44.9) EBRT: 53 (12.2) BT: 45 (10.4) AS: 141 (32.5)	12	NR	<5: 49 (11%) 5–9.9: 248 (57%) ≥10: 137 (32%)	6: 264 (64) 7: 151 (36)	LR: 181 (42) IR: 199 (46) HR: 54 (12)
Kao 2021 [30]	PLS	196	RP: 104 (53) RT: 37 (18.8) AS: 55 (28)	NR	69	NR	NR	LR: 43 (22) IR: 72 (37) HR: 81 (41)
Luckenbaugh 2022 [31]	PLS	2742	RP: 1419 (51.8) RT: 630 (23) RT+ADT 321 (11.7) AS: 372 (13.7)	60	65 (57–74)	RP: 5.1 (4.2–6.8) RT: 7 (4.9–11.3) RT+ADT: 5.5 (4.3-7.3) AS: 5.2 (3.9-7)	6: 1425 (52) 3+4: 780 (28.4) 4+3: 268 (9.8) ≥8: 258 (9.4)	LR: 1240 (45.2) IR: 1070 (39) HR: 424 (15.5)
Tiruye 2022 [32]	PLS	4926	RP: 2810 (57) EBRT: 1011 (20.5) BT: 343 (7) AS: 762 (15.5)	12	66.1 (7.7)	<4: 534 (10.8%) 4–10: 2768 (56.2%) 10–20: 812 (16.5%) >20: 272 (5.5%)	≤6: 1513 (30.7) 3+4: 1543 (31.3) 4+3: 880 (17.9) ≥8: 927 (18.8)	LR: 1137 (23.1) IR: 2043 (41.5) HR: 1517 (30.8)
Kord 2023 [33]	PLS	1012	RP: 557 (55) RT: 203 (20) AS: 252 (25)	60	61.6 (7.5)	5.4 (2.9)	NR	LR: 614 (60.7) IR: 298 (39.3)
Smith 2010 [34]	PPS	1636	RP: 981 (60) EBRT: 123 (7.5) EBRT + ADT 166 (10.1) LDR-BT: 58 (3.5) HDR-BT 47 (2.9) AS: 200 (12.2) Other: 61 (3.7)	36	61.2 (61-61.5)	7.7 (0.2–602)	≤6: 894 (55) 7: 557 (34.3) ≥8: 173 (10.7)	NR
Chen 2017 [35]	PPS	1141	RP: 469 (41.1) EBRT: 249 (21.8) BT: 109 (9.6) AS: 314 (27.5)	24	65	0–9.9: 961 (85.4%) 10–20: 102 (9.1%) ≥20: 63 (5.6%)	≤6: 653 (57.8) 7: 390 (34.5) 8–10: 87 (7.7)	NR
Wallis 2022 [36]	PPS	2072	RP: 1136 (55) RT: 667 (32) AS: 269 (13)	60	64 (59–69)	<4: 402 (19%) 4–10: 1431 (69%) 10–20: 183 (9%) 20–50: 56 (3%)	≤6: 1081 (52) 3 + 4: 584 (28) 4 + 3: 200 (10) ≥8: 199 (10)	LR: 951 (46) IR: 794 (38) HR: 321 (16)
Vanagas 2013 [37]	CSS	501	RP: 92 (18.4) RT: 73 (14.6) AS: 61 (12.2) Other: 275 (54.8)	NR	≤63: 119 (25.5%) 64–75: 221 (47.5%) ≥75: 126 (27%)	NR	NR	NR

Table 2 (**continued**)

Study	Design	Pts	Interventions, *n* (%)	FU (mo)	Age (yr) [b]	pPSA (ng/ml) [c]	GS, *n* (%)	Risk group, *n* (%)
Venderbos 2017 [38]	CSS	408	RP: 69 (16.9) RT: 219 (53.7) AS: 120 (29.4)	79 [a] (48–120)	RP: 76.0 (2.6) RT: 74.5 (6.4) AS: 71.9 (6.4)	RP: 7.3 (6.1) RT: 7.5 (3.1) AS: 5.9 (3.1)	≤6: 342 (83.8) 7: 38 (9.3)	NR
Sureda 2019 [39]	CSS	396	RP: 99 (25) EBRT: 99 (25) BT: 99 (25) AS: 99 (25)	36	RP: 68.2 (5.4) EBRT: 73.2 (5.3) BT :71.9 (5.0) AS: 70.6 (5.4)	RP: 7.3 (2.8) EBRT: 7.7 (3.0) BT: 7.6 (2.6) AS: 6.8 (2.9)	≤6: 349 (88.1) 3+4: 47 (11.9)	LR: 296 (74.7) IR: 100 (25.3)
Bergius 2020 [40]	CSS	867	RP: 299 (34.5) RT: 280 (32.2) AS: 226 (26.1) Other: 62 (7.2)	24	66.9	NR	Mean: GS 6.81	NR
Venderbos 2021 [24]	CSS	2943	RP: 1101 (37.4) RT: 304 (10.3) AS: 179 (6.1) Other: 1359 (46.2)	NR	71 (65–75)	NR	≤6: 317 (10.8) 3 + 4: 538 (18.3) 4 + 3: 355 (12.1) ≥8: 584 (19.8)	NR

RCT = randomized controlled trial; PLS = prospective longitudinal study; PPS = population-based prospective study; CSS = cross-sectional study; Pts = patients; RP = radical prostatectomy; ORP = open RP; RARP = robot-assisted RP; RT = radiotherapy; EBRT = external beam RT; BT = brachytherapy; LDR = low dose rate; HDR = high dose rate; AS = active surveillance; ADT = androgen deprivation therapy; FU = follow-up; NR = not reported; pPSA = preprocedural prostate-specific antigen; GS = Gleason score; LR = low risk; IR = intermediate risk; HR = high risk.

[a] Median (range).

[b] Reported as the mean (standard deviation) or median (range or interquartile range).

[c] Reported as the mean (standard deviation) or median (range or interquartile range) or the distribution by category.

All studies included in the review consistently revealed that RP has a greater adverse effect on continence in comparison to RT and AS, especially in the early period after treatment. Thereafter, continence tended to improve over time, stabilizing at UI rates that were superior to those after other treatments in all studies [7,8,24,29,32,33,38,41]. Although EBRT does not seem to significantly affect continence, in some studies BT was associated with continence rates that, even if not comparable to those after RP, should be taken into consideration when counseling patients before treatment [27,29].

3.2.3. *PROMs for sexual function*

Seventeen papers provided data on sexual function that were measured using different PROM tools. Of these, two were RCTs, while the others were prospective observational or cross-sectional studies. The questionnaire most frequently to assess sexual function was EPIC-26 (12 papers); other tools used were the EORTC QLQ-PR25, PCSI, UCLA-PCI, and the 15 Dimensions questionnaire.

Among the functional domains, greatest impairment was reported for sexual function. A decrease in erectile function was observed after all treatment modalities, and sexual side effects related to radical treatments were more immediate and persistent over time. Among the various treatments, RP led to the greatest deterioration in sexual function over time in all the studies, while the deterioration with AS was the least evident, but gradually developed over time.

Approximately 15% of patients who underwent RP reported poor erections at baseline, in comparison to 30–40% of patients undergoing RT [42], probably because of differences in age and comorbidities among patients selected to undergo these treatments. After RP, up to 80–90% of patients reported erectile dysfunction [42,47], decreasing to approximately 60% by 2 yr [42,50]. After RT there was an increase in erectile function over time (up to 50–60% for EBRT and 20–50% for BT at 2 yr) [42,47,50–52]. As expected, AS was the treatment with less of an effect on erectile function, although a steady decline in sexual function was largely reported [7,19,28,35]. This constant and progressive decline confirms that not only the type of treatment received but also aging and other factors are implicated in the genesis of erectile dysfunction.

3.2.4. *PROMs for bowel function*

Sixteen studies reported PROMs assessing bowel function using several different questionnaires. Among these, EPIC-26 (considering both the bowel function domain and bowel summary score) was the most commonly used (12 papers), while a minor number of studies reported results for UCLA-PCI bowel function, PCSI bowel problems, or EORTC QLQ-PR25 bowel-related symptoms.

Despite the relatively high number of studies reporting PROMs for bowel function, there is no consensus on the effect of different treatments on bowel function, as only a small proportion of the studies found significant differences for this domain. Nevertheless, worsening of bowel function was generally observed for patients treated with RT, with 15–40% of patients who underwent EBRT or BT reporting acute bowel bother after radiation, with subsequent good recovery for the BT group (<10% reporting symptoms at 2 yr) and less so after EBRT [42,47,49]; no significant differences were reported for RP or AS.

3.2.5. *PROMs for QoL*

Sixteen studies comparing different treatments for localized PCa reported data on QoL using validated PROMs. Of these, two were RCTs (data from the ProtecT trial), five were cross-sectional studies, eight were longitudinal prospective studies, and one was a population-based prospective study.

There was heterogeneity in PROM tools used report QoL in the studies. Most studies found no significant differences among the treatment groups, except for patients receiving hormonal therapy or chemotherapy, who reported greater

Table 3 – Overview of PREMs assessed in the studies included in the systematic review

Study	PREMs	PREM results		
		RP	RT	AS
Ernstmann 2012 [26]	Generic psychosocial care instrument Mean score at diagnosis vs 6 mo			
	Devotion by physicians	2.46 vs 2.43	2.54 vs 2.33	2.77 vs 2.51
	Support by physicians	3.39 vs 3.37	3.45 vs 3.32	3.58 vs 3.68
	Info from physicians	3.76 vs 3.66	3.72 vs 3.67	3.75 vs 3.81
	Shared decision-making	3.34 vs 3.14	3.44 vs 3.00	3.48 vs 3.42
van Stam 2020 [29]	Decision Regret Scale [a] Patients with a score ≥26	23%	EBRT 37%, BT 18%	20%
Luckenbaugh 2022 [31]	Social support, median score (range)	95 (75–100)	RT: 95 (70–100) RT+ADT 95 (75–100)	95 (75–100)
	Participatory decision making, median score (range)	86 (71–93)	RT: 79 (68–92) RT+ADT: 79 (64–89)	86 (68–96)
Wallis 2022 [36]	Validated PCa-oriented scale of Clark Patients with TRR at 5 yr, % (95% CI)	16% (14–18%)	11% (9–14%)	7% (4–11%)

ADT = androgen deprivation therapy; AS = active surveillance; BT = brachytherapy; CI = confidence interval; EBRT = external beam RT; PCa = prostate cancer; PREM = patient-reported experience measure; RP = radical prostatectomy; RT = radiation therapy; TRR = treatment related regret.
[a] A score ≥26 represents a clinically relevant level of regret: score ≥26).

anxiety/depression and worse QoL scores, probably because of more advanced disease [7,8,24,34,37–40].

3.3. PREMs after AS versus RT versus RP

Only three prospective observational studies reported PREMs [26,29,36] and used different tools.

In a population-based prospective cohort study, Wallis et al [36] retrospectively analyzed PREMs from 2072 PCa patients treated with either RP, RT, or AS between 2011 and 2012, using the validated PCa-oriented scale of Clark to assess treatment-related regret. The authors concluded that more than 10% of patients with localized PCa experience treatment-related regret, at rates that differ by treatment modality, according to functional outcomes and patient expectations. The treatment-related regret at 5 yr was 16% for RP, 11% for RT, and 7% for AS. van Stam et al [29] conducted a prospective multicenter study involving 434 men treated with AS, RP, EBRT, or BT between 2014 and 2016. Decision regret was assessed at 3, 6, and 12 mo and was relatively frequent among patients experiencing unwanted physical, psychosocial, and oncological outcomes, irrespective of the treatment modality, with 23% of the patients reporting clinically relevant treatment regret. Finally, Ernstmann et al [26] reported results for a generic psychosocial care instrument assessed at 6 mo in a prospective observational cohort of 1216 patients treated with ADT, AS, RT, RP, or watchful waiting. A significant decline in shared decision-making behavior by physicians for the RP and ADT groups was reported between initial diagnosis and 6 mo after treatment. In terms of emotional support from physicians, there was a significant difference between treatment groups at the time of initial diagnosis, with patients in the RP group reporting significantly less support than the ADT group.

4. Discussion

To the best of our knowledge, this is the most comprehensive review to date exploring PROMs and PREMs in prospective comparative studies that included all guideline-recommended treatment options for localized PCa. Our review offers clinically meaningful insights for patients, clinicians, and policymakers.

A first key finding of our review is that although PROMs and PREMs are fundamental tools for selection of the best management strategy for localized PCa via shared decision-making [11,53], there is a relative lack of prospective comparative clinical trials assessing PROMs and PREMs after RP, RT, or AS for localized PCa. We were only able to include one RCT in the review, and several heterogeneous instruments were used to report PROMs/PREMs in the studies available (Table 1).

A second key finding of our review is that according to the best available evidence (prospective comparative studies including all management options recommended by international guidelines [1]), all strategies for localized PCa have an impact on PROMs and PREMs, each with a specific profile (Supplementary Tables 2–4 and Fig. 2), expect for mental and physical QoL in most of the studies. Of note, the outcomes considered in this review were reported by patients, stressing the importance of incorporating their perspective in shared decision-making and of critically evaluating previous literature on functional outcomes after AS, RP, or RT that were assessed by clinicians [54,55]. Importantly, among the few studies assessing PREMs, a non-negligible proportion of patients reported decisional regret, irrespective of the treatment modality.

When considering treatment-related morbidity and PROMs/PREMs, the length of follow-up and physiological aging of patients, which inevitably leads to a deterioration in functional outcomes in addition to the effect of the treatment itself, must be taken into account. As reported by Donovan et al [23] for a recent analysis of ProtecT data at 12-yr follow-up, effects on sexual, urinary, and bowel function persist in a non-negligible number of patients and can worsen over time. Their analysis revealed that urinary leakage continued to mostly affect the RP group over 7–12 yr of follow-up, with twice as many RP patients (18–24%) requiring pads in comparison to AS (9–11%) and RT (3–8%). While

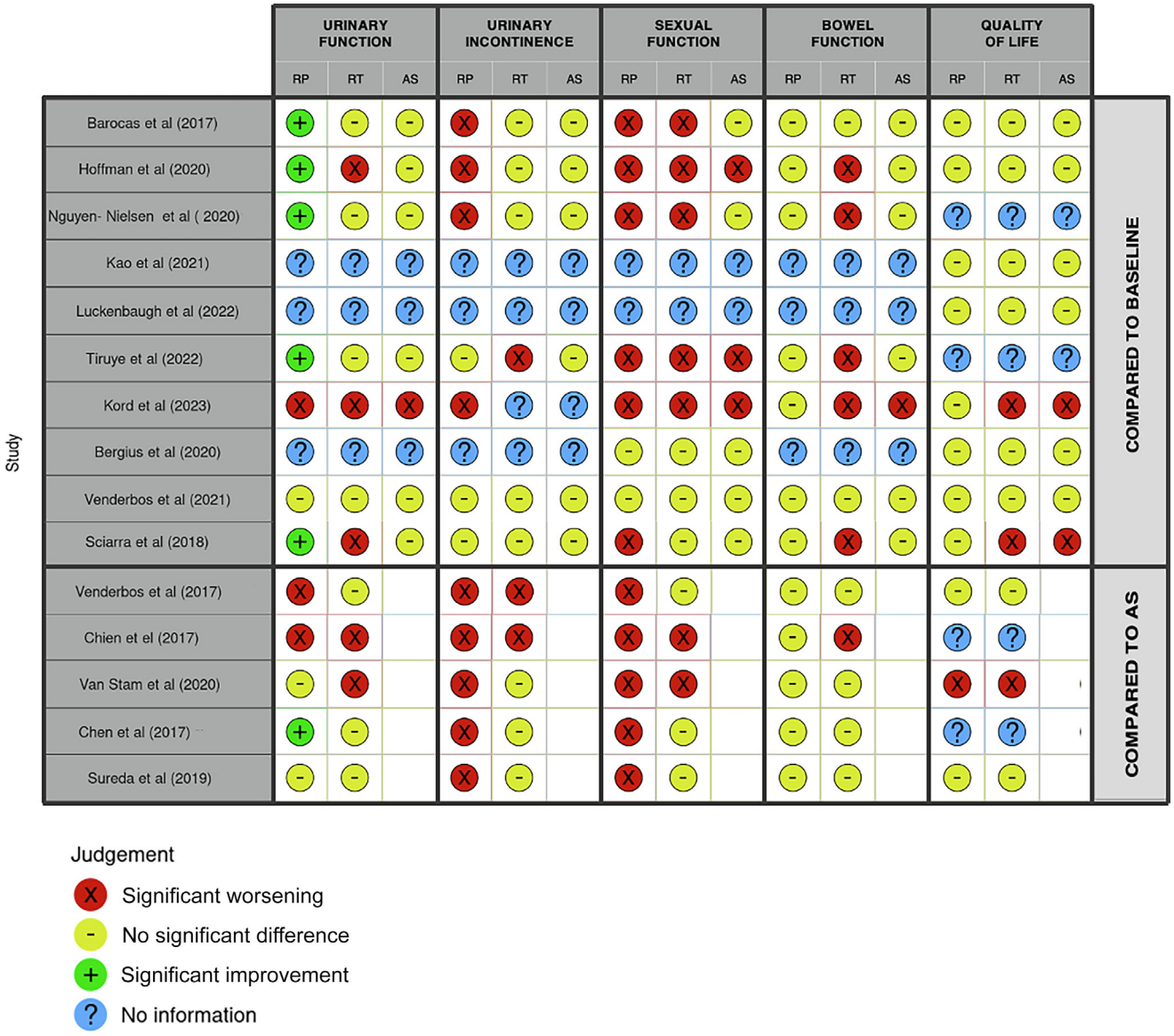

Fig. 2 – Effect of treatments on functional domains and quality of life. Summary overview of the effect of the different treatments on functional domains (urinary function, urinary incontinence, sexual function, bowel function) and quality of life in the studies included in the review. The first column shows the study and year of publication. Five columns report the domain assessed, each divided into the three treatments considered (RP, RT, and AS) to evaluate the comparative effect of each modality on the individual outcome (as reported at last follow-up in each study). Studies were divided according to whether the effects on the various domains were compared to the patient's respective baseline data, or whether the PROMs referring to RP or RT were compared to AS (considered as a "control group"). Judgment was reported according to a color code, taking inspiration from the classical risk-of-bias assessment figure, as follows (considering whether the finding was statistically significant in each study): Red = statistically significant post-treatment worsening of PROMs at last follow-up, for each treatment option, as compared to baseline or to AS; yellow = no statistically significant difference in PROMs at last follow-up, as compared to baseline or to AS; green = statistically significant post-treatment improvement in PROMs at last follow-up, as compared to baseline or to AS; blue = lack of specific information or PROM assessment.

sexual function reached a similarly low level in all groups by year 12, the RP group experienced the worst impact, with minimal recovery after the initial impact of surgery and then a further slow decline. The RT and AS groups experienced a similar gradual decline over time [23]. This highlights the need for long-term follow-up of PROMs to allow full consideration of the trade-offs between the benefits and harms of treatments, particularly in light of the high likelihood of long-term survival.

Taken together, our findings support a need to set realistic expectations when counseling patients with localized PCa and to use a patient-centered, individualized shared decision-making approach when selecting the right treatment for the right patient.

Our systematic review provides a foundation for significant further research in this field. First, PROMs and PREMs should be integrated in future composite outcome measures (overcoming the classical trifecta and pentafecta con-

cepts, which have only been applied to RP series and did not include any patient-centered perspective) [56,57]. Standardization of PROM/PREM reporting is also urgently warranted for clinical trial design, especially considering the novel treatment strategies increasingly being adopted for localized PCa, such as focal therapy [58–60]. In attempts to standardize the definition, collection, and analysis of PROMs, the SISAQOL-IMI Consortium [53] and PIONEER Consortium [58,61] recently recommended the EORTC QLQ-C30 and EORTC QLQ-PR25 as items to use in both research and routine care settings. Similarly, EPIC-26 [62] was selected by the International Consortium on Health Outcomes Measurement as part of the standard set of data that should be collected for each patient with clinically localized PCa [63]. Moreover, a US National Cancer Institute working group stated that additional domains of interest should include decisional regret, satisfaction with care, and anxiety or worry about PCa and disease progression [64]. Treatment-related regret captures the effect of both treatment-related morbidity and anxiety associated with PCa diagnosis and treatment [36].

Beyond PROMs and PREMs, future studies should also encompass caregiver-reported outcome measures (CROMs), as caregiver QoL is also influenced by the patients' burden of disease [65]. So far, only a few studies have reported such data and no psychometrically validated CROMs are available [66], so further work is undoubtedly needed to validate tools to measure CROMs.

While our findings should be interpreted in light of specific limitations at both the study and review level (Supplementary material), they shed light on distinct unmet clinical needs in this area and pave the way to improvements in reporting of PROMs and PREMs in daily clinical practice, with the ultimate goal of optimizing shared decision-making and individualized value-based care for patients with PCa.

5. Conclusions

As several management options are currently recommended for patients with clinically localized PCa (including RP, RT, and AS) with comparable long-term oncological outcomes, PROMs and PREMs are becoming critical factors in informing shared decision-making.

Our systematic review found significant heterogeneity in the reporting of PROMs and PREMs, so standardization of PROM and PREM assessment in real-world practice and clinical trials is warranted.

According to the evidence available for PROMs, RP has to have a higher UI rate and a greater impact on sexual function in comparison to other options, but is associated with a lower scores for the lower urinary tract symptoms domain. Conversely, RT (in particular BT) is associated with higher bother scores for voiding symptoms and bowel function, although the latter is still controversial in light of conflicting data. Lastly, while none of the management options had a significant impact on mental or physical QoL, AS was more commonly associated with emotional distress. Only a few studies reported on PREMs and showed non-negligible rates of decision regret, highlighting an unmet need that should be explored more thoroughly in future studies.

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Analysis and interpretation of data: Campi, Alberti, Nicoletti, Castellani.
Drafting of the manuscript: Campi, Alberti, Nicoletti, Castellani, Maggi, Dibilio, Resta, Makrides.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.05.008.

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