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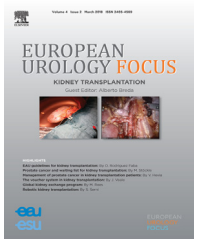

Review – Prostate Cancer

Health-related Quality of Life in Patients with Advanced Prostate Cancer: A Systematic Review

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Abstract

Context: The assessment of "soft" endpoints such as health-related quality of life (HRQOL) is increasingly relevant when evaluating the optimal treatment sequence of novel therapeutic options in patients with advanced prostate cancer (PCa).
Objective: To systematically review contemporary data regarding HRQOL outcomes in patients with advanced PCa.
Evidence acquisition: A systematic review of the literature published between January 2011 and March 2019 was performed using the PubMed/Medline Database. In total, 873 articles were screened, and 14 articles including 12 661 patients were selected for synthesis and included in the current analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and European Association of Urology recommendations.
Evidence synthesis: Regarding HRQOL assessment, the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire was used in 11 of 14 studies, the European Quality of Life 5-Dimensions (EQ-5D) questionnaire in six of 14 studies, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) in two of 14, and its prostate-specific amendment QLQ-PR25 was used in one of 14 studies. Three studies included patients with metastatic castration-sensitive prostate PCa, and found beneficial HRQOL effects for abiraterone acetate and docetaxel compared

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Functional Assessment of Cancer Therapy-Prostate
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
European Quality of Life 5-Dimensions

with standard androgen deprivation therapy. Two studies included patients with nonmetastatic castration-resistant PCa, and positive HRQOL effects for enzalutamide and apalutamide were observed. Nine studies focused on patients with metastatic castration-resistant PCa. Hereby, beneficial HRQOL outcomes were described for enzalutamide, abiraterone acetate, and radium-223. Evidence synthesis was mostly based on studies with a low risk of bias based on standardized risk of bias assessment. Limitations include hampered comparability between different validated questionnaires, lack of baseline values, and unclear impact of supportive care on HRQOL outcomes.

Conclusions: There is strong evidence from several phase III trials supporting a beneficial effect of current systemic treatment options on HRQOL outcomes in patients with advanced PCa compared with standard androgen deprivation therapy.

Patient summary: In this systematic review, we provide an overview of contemporary data from large clinical trials on the effect of current treatment strategies on patients' health-related quality of life (HRQOL). We summarize the assessment tools that have been used to measure HRQOL and show that there are robust data for positive HRQOL effects of numerous agents in different clinical stages of advanced prostate cancer.

1. Introduction

Since the introduction of taxane-based chemohormonal therapy in the early 2000s [1,2], a multitude of new agents has been introduced as therapeutic options, next to standard androgen deprivation therapy (ADT), for different stages of advanced prostate cancer (PCa), defined as metastatic hormone-naive prostate cancer (mHNPC), nonmetastatic castration-resistant prostate cancer (nmCRPC), or metastatic castration-resistant prostate cancer (mCRPC). These current therapeutic options include docetaxel (mHNPC and mCRPC) [3] abiraterone acetate (mHNPC and mCRPC) [4], enzalutamide (nmCRPC and mCRPC) [5], Ra-223 (mCRPC) [6], and more recently apalutamide (nmCRPC) [7], as well as darolutamide (nmCRPC; approved by the Food and Drug Administration, but not yet approved by the European Medicines Agency) [8]. With a plethora of treatment options being available, it has been postulated that optimal stratification and sequencing of the therapeutic strategies should be focused on individual risk profiles as well as health-related quality of life (HRQOL), since all the treatment modalities, while proved to be efficient, have the potential to induce side effects and consequently deteriorate HRQOL.

In addition, health-care systems nowadays put greater emphasis on patient-reported outcomes (PROMS), which indicate individual subjective patients' experience of the respective treatment, reflecting the growing interest of incorporating PROMS into modern state-of-the-art cancer care [9].

It has become common to report PROMS based on objective validated questionnaires, and HRQOL data are accessible for all the abovementioned treatment options. The aim of this article was to systematically address HRQOL outcomes of contemporary randomized trials, assessing the efficacy of novel systemic therapies in patients with advanced PCa (namely, metastatic or nonmetastatic castration-resistant disease).

2. Evidence acquisition

We performed a systematic review of the literature up to March 2019, starting from January 2011, using the PubMed, Web of Sciences, and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Inclusion criteria encompassed patients with advanced PCa, defined as mHNPC, nmCRPC, and mCRPC. In order to be eligible for the systematic review, studies had to be at least phase II, enroll a minimum of 100 patients, and focus on advanced PCa only. HRQOL had to be assessed via a standardized, validated HRQOL-specific tool. For phase II trials, HRQOL had to be a prespecified primary endpoint, and for large phase III trials, HRQOL was accepted as a secondary endpoint. Search results were restricted to English language. Keywords arranged in variable combinations included "health related quality of life," "prostate cancer," "advanced," and "metastatic." Reference lists of included articles were screened for relevant articles, and additional references were identified. Two authors (A.K. and D.T.) independently selected eligible studies. Discrepancies between the two authors were resolved via consensus. The primary endpoint was HRQOL based on validated questionnaire scores. The study selection process is shown in the PRISMA diagram (Fig. 1). In total, 873 articles were screened and 14 articles were included in the systematic review.

3. Evidence synthesis

3.1. Study selection and quality assessment

Overall, 14 studies evaluating HRQOL in 12 661 patients were included in the evidence synthesis. Identified articles were assessed for the risk of bias following current European Association of Urology instructions [10]. A summary of risk of bias assessments is provided in Fig. 2.

3.2. Validated questionnaires

Multiple validated questionnaires addressing multiple aspects of HRQOL have been used in the articles that were assessed in the current systematic review.

In the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, 27 cancer-specific domains that are

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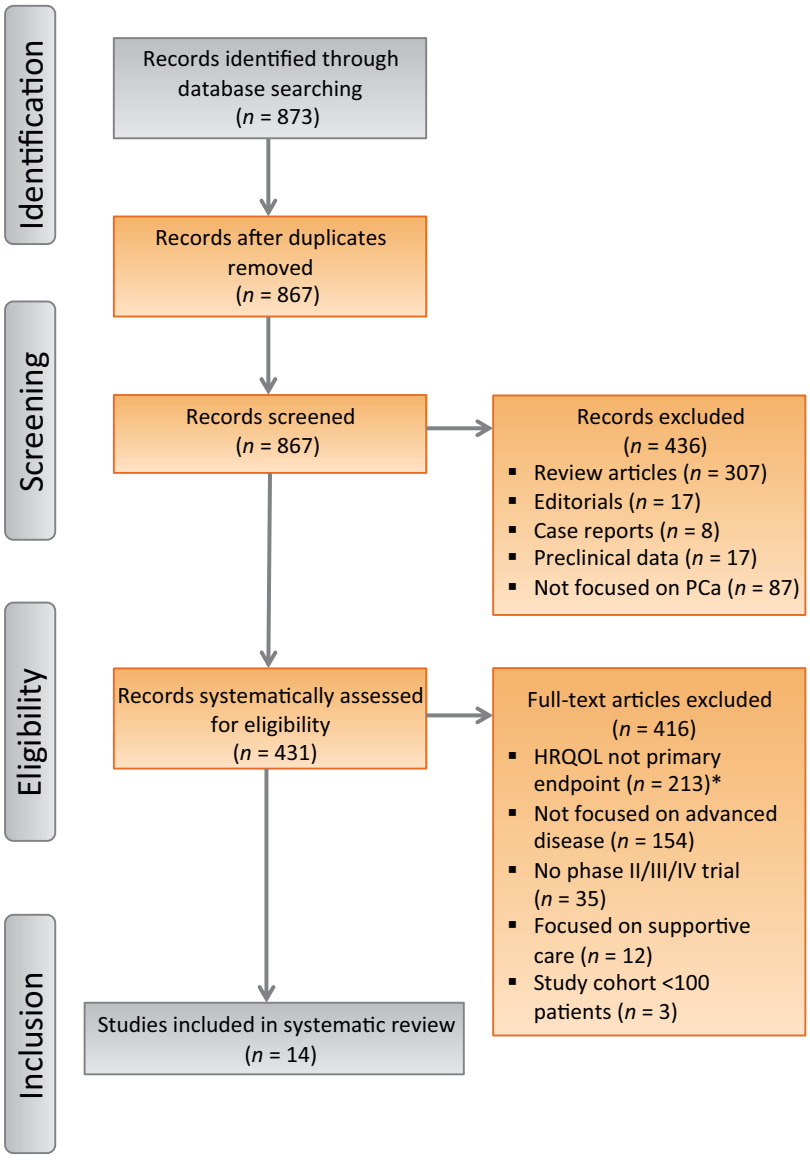

Fig. 1 – Summary of evidence acquisition following the PRISMA guidelines. HRQOL = health-related quality of life; PCa = prostate cancer; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis (*only for phase II trials).

subdivided into four domains (physical well-being [seven items], social or family well-being [seven items], emotional well-being [six items], and functional well-being [seven items]) are reported. In addition, there are 12 PCa-specific items. Function during the previous week is assessed. The subscales and items are rated from 0 ("not at all") to 4 ("very much"). In addition, a FACT-P total score can be calculated by adding the abovementioned items together. The FACT-P total score can range from 0 to 156. Hereby, higher scores represent better HRQOL [11]. Of the 14 studies included in the current systematic review, 11 used the FACT-P questionnaire.

The European Quality of Life 5-Dimensions (EQ-5D) questionnaire has originally been designed to evaluate generic HRQOL, and includes subdomains such as the utility index (five items) and a visual analog scale ranging from 0 ("worst imaginable") to 100 ("best imaginable") [12]. To date, many modifications of the original version, for instance, the EQ-5D-5L questionnaire [13], exist. In the current systematic review, six studies used the EQ-5D questionnaire or one of its modifications.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) focuses on several HRQOL aspects of cancer patients and is not PCa specific. It comprises five functional scales (physical, role, cognitive, emotional, and social) and three symptom scales (fatigue, pain, and nausea and vomiting). In addition, several single items regarding symptoms as well as financial difficulties are addressed. Importantly, the questionnaire also addresses the global health status that represents general HRQOL [14]. In the current systematic review, two studies used the QLQ-C30 questionnaire. The original QLQ-C30 questionnaire has been complemented with a PCa-specific module (EORTC QLQ-PR25) that has been

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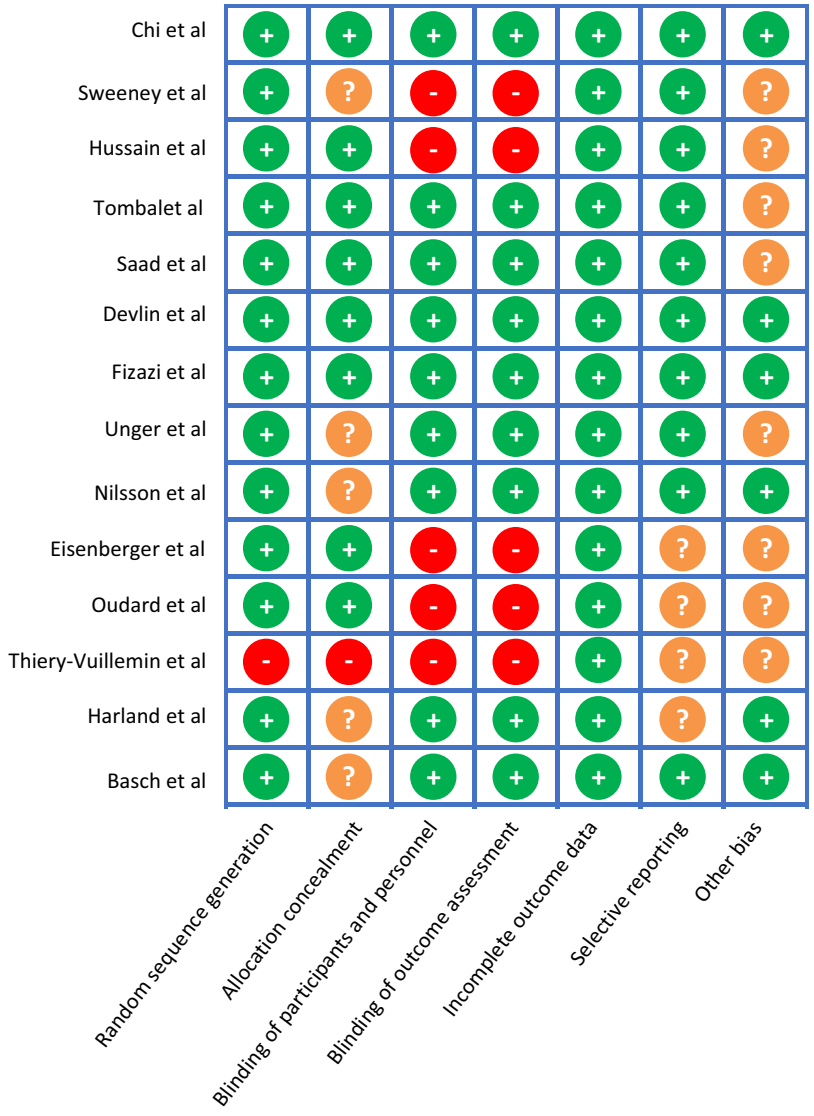

Fig. 2 – Risk of bias assessment following current EAU recommendations. EAU = European Association of Urology.

designed to assess HRQOL specifically in patients with PCa. It consists of questions addressing urinary symptoms (eight items), bowel symptoms (four items), and hormone therapy-related symptoms (six items) in the previous week. Patients are instructed to rate the respective items from 1 ("not at all") to 4 ("very much"). Hereby, higher scores reflect a greater number of symptoms [15]. In the current systematic review, one out of 14 studies used the EORTC QLQ-PR25 questionnaire.

3.3. *Metastatic hormone-naive prostate cancer*

Recently, HRQOL outcomes of three randomized controlled phase III trials have been published. The main features of each study are summarized chronologically in Table 1.

Hussain et al [16] randomized 1535 patients with newly diagnosed mHNPC to receive either continuous or intermittent ADT. HRQOL outcomes were assessed based on the SWOG HRQOL questionnaire. Net differences in physical functioning favored patients undergoing intermittent ADT (–2.68 vs –5.72, $p = 0.04$), as did vitality, libido, and mental health, without reaching statistical significance. Since the study was designed as open label, risk of bias assessment showed mixed results with a tendency toward a low risk of bias (Fig. 2).

The randomized controlled phase III LATITUDE trial analyzed oncological [17] as well as HRQOL outcomes [18] in 1199 patients with newly diagnosed high-risk mHNPC. Risk assessment was performed based on Gleason grading as well as PSA doubling time. Patients were randomly assigned to receive standard ADT in combination with placebo or in combination with abiraterone acetate 1000 mg daily (in combination with 5 mg prednisone daily). Regarding HRQOL outcomes, EQ-5D-5L and FACT-P questionnaires were used, and 10% of the data were missing. Regarding general HRQOL, as assessed by the FACT-P total score, the authors found increased time to deterioration of FACT-P total scores for patients who underwent treatment with

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Table 1 – Main features of studies addressing patients with metastatic hormone naive prostate cancer.

Study	Intervention	Phase	*n*	Follow-up	Tool	HRQOL baseline	Main findings
Hussain et al (2013) [16]	IADT vs CADT	III	1162	Up to 15 mo	SWOG QOL questionnaire	NR	Net differences in primary SWOG QOL outcomes after 15 mo: erectile dysfunction −3% (IADT) vs 2% (CADT), p = 0.12; high libido 13% (IADT) vs 3% (CADT), p = 0.46; vitality −2.02 (IADT) vs −3.02 (CADT), p = 0.45; mental health −0.64 (IADT) vs −1.10 (CADT), p = 0.69; physical functioning −2.68 (IADT) vs −5.72 (CADT), p = 0.04
Chi et al (2018) [18] (LATITUDE)	ABI vs PBO	III	1199	Median 30.9 mo (ABI) vs 29.7 mo (PBO)	FACT-P EQ-5D (−5 L)	FACT-P (total): ABI: 113 PBO: 112 EQ-5D−5 L (VAS): ABI: 74 PBO: 74	Median time to deterioration of FACT-P total score 12.9 mo (ABI) vs 8.3 mo (PBO), HR 0.85, 95% CI 0.74–0.99, p = 0.032; EQ-5D VAS: better general health status for ABI vs PBO, same findings for EQ-5D utility score
Morgans et al (2018) [19] (E3805 CHAARTED)	DOC + ADT vs ADT	III	790	Up to 12 mo	FACT-P (FACT-Taxane)	FACT-P (total): DOC: 119 ADT: 119	Net differences in FACT-P total scores after 3 mo: −2.7 (DOC) vs −1.1 (ADT), p = 0.02; net differences in FACT-P total scores after 12 mo: −0.7 (DOC) vs −4.2 (ADT), p = 0.04; changes not considered clinically meaningful

ABI = abiraterone acetate; ADT = androgen deprivation therapy; CADT = continuous androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; EQ-5D = European Quality of Life 5-Dimensions; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; HRQOL = health-related quality of life; IADT = intermittent androgen deprivation therapy; NR = not reported; PBO = placebo; QOL = quality of life; VAS = visual analog scale.

abiraterone acetate (8.3 vs 12.9 mo, hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74–0.99, $p = 0.032$). Similar results were found for remaining subscales [18]. These findings have a low risk of bias (Fig. 2).

The CHAARTED study reported oncological [3] as well as HRQOL outcomes [19] of 790 patients with mHNPC who were randomly assigned to receive either ADT or ADT in combination with docetaxel 75 mg/m^2. HRQOL assessment was based on the FACT-P questionnaire. Missing data were up to 23% at the 12-mo assessment. The authors found a significant decline in FACT-P total scores after 3 mo for patients who underwent combination therapy ($p < 0.001$), with a consecutive rise in the longer-term assessment up to 12 mo. Consequently, patients receiving docetaxel showed significantly lower FACT-P total scores than patients with ADT monotherapy after 3 mo (net differences −2.7 vs −1.1, $p = 0.02$), but significantly higher FACT-P total scores after 12 mo (net differences −0.7 vs −4.2, $p = 0.04$). Notably, CHAARTED was an open-label study. Thus, as illustrated in Fig. 2, risk of bias assessment showed mixed results, especially regarding detection as well as performance bias. Notably, baseline FACT-P total scores were slightly higher within the CHAARTED [19] than in the LATITUDE cohort [17].

3.4. *Nonmetastatic castration-resistant prostate cancer*

Recently, two randomized controlled phase III trials reported oncological [7,20] as well as HRQOL [21,22] outcomes for patients with high-risk nmCRPC. After inclusion in the PROSPER trial, patients received either enzalutamide 160 mg/d or placebo combined with standard ADT, whereas in SPARTAN, patients received the next-generation androgen inhibitor apalutamide 240 mg/d or placebo in combination with standard ADT. Of note, both PROSPER and SPARTAN included only asymptomatic patients. Thus, HRQOL preservation is of utmost importance in these patients. The main features of both studies are summarized chronologically in Table 2.

PROSPER randomized a total number of 1401 patients; HRQOL outcomes were analyzed using the FACT-P questionnaire, QLQ PR-25 (focus on hormonal symptoms), and EQ-5D (-5L) questionnaires [22]. In line, SPARTAN randomized 1207 patients and focused on the FACT-P and EQ-5D (-3L) questionnaires [21]. Briefly, both studies confirmed preservation of general HRQOL based on FACT-P total scores for combination with enzalutamide (net difference −7.17 [enzalutamide] vs −9.20 [placebo], $p = 0.184$) or apalutamide (net difference 1.8 [apalutamide] vs −3.3 [placebo] before symptomatic progressive disease). As illustrated in Fig. 2, both studies imply a low risk of bias. Baseline FACT-P total scores were slightly higher within the PROSPER [22] than in the SPARTAN [21] cohort.

3.5. *Metastatic castration-resistant prostate cancer*

Several studies have reported HRQOL outcomes in mCRPC patients. The main features of each study included in the

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Table 2 – Main features of studies addressing patients with nonmetastatic castration-resistant prostate cancer.

Study	Intervention	Phase	*n*	Follow-up	Tool	HRQOL baseline	Main findings
Saad et al (2018) [21] (SPARTAN)	APA vs PBO	III	1207	Median 20.3 mo	FACT-P 5Q-5D (−3 L)	FACT-P (total): APA: 116 PBO: 119 EQ-5D−3 L (health status score): APA: 76.2 PBO: 76.8	Net difference in FACT-P total scores: 2.00 (APA) vs −1.4 (PBO) before metastasis, −3.4 (APA) vs 4.8 (PBO) after metastasis, 1.8 (APA) vs −3.3 (PBO) before symptomatic progressive disease, and −6.6 (APA) vs −12.2 (PBO) after symptomatic progressive disease
Tombal et al (2019) [22] (PROSPER)	ENZA vs PBO	III	1401	Median 18.5 mo (ENZA), 15.1 mo (PBO)	FACT-P QLQ-PR25 EQ-5D (−5 L)	FACT-P (total): ENZA: 120 PBO: 121 QLQ-PR25 (hormonal symptoms): ENZA: 14.9 PBO 15.79 EQ-5D−5 L VAS: NR	At week 97, net difference in FACT-P total scores: −7.17 (ENZA) vs −9.20 (PBO), $p = 0.184$; no difference in prostate cancer pain subscale. Net difference in QLQ-PR25 hormonal treatment-related symptoms scores: 1.55 (ENZA) vs −1.83 (PBO), $p = 0.0020$; no differences in urinary and bowel symptoms scores. No differences in mean differences of EQ-5D−5 L VAS scores ($p = 0.639$)

APA = apalutamide; ENZA = enzalutamide; EQ-5D = European Quality of Life 5-Dimensions; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HRQOL = health-related quality of life; NR = not reported; PBO = placebo; VAS = visual analog scale.

systematic review are summarized chronologically in Table 3.

The oncological effect of abiraterone acetate in patients with mCRPC has been evaluated in the postchemotherapy setting [4] as well as in chemotherapy-naïve patients [23]. For both studies, HRQOL has been reported. Harland et al [24] analyzed HRQOL outcomes of 1395 patients using the FACT-P questionnaire. The authors found significant improvements in FACT-P total scores in 48% of patients receiving abiraterone acetate in combination with 10 mg prednisone daily versus 32% receiving placebo ($p < 0.0001$). In addition, the median time to deterioration in Fact-P total score was 59.9 wk for the abiraterone subgroup compared with 36.1 wk for the placebo subgroup ($p < 0.0001$). No baseline values of FACT-P total scores were reported. As shown in Fig. 2, the risk of bias was generally low.

Regarding the effect of abiraterone acetate in chemotherapy-naïve patients, Basch et al [25] reported HRQOL outcomes of 1088 patients. General HRQOL was assessed using the FACT-P questionnaire, and baseline FACT-P total scores were reported. The median time to deterioration in FACT-P total scores was 12.7 mo for the abiraterone subgroup versus 8.3 mo for the placebo subgroup ($p = 0.003$). The median time to deterioration in FACT PCa subscale was 11.1 versus 5.8 mo ($p < 0.0001$) [25]. The risk of bias was mostly low (Fig. 2).

The impact of the potent androgen inhibitor enzalutamide on HRQOL has been tested in mCRPC patients both in the postchemotherapy [26,27] and in the prechemotherapy setting [28].

In the AFFIRM trial, 1199 patients with mCRPC who had already been treated with chemotherapy were randomized to receive either enzalutamide 160 mg/d or placebo in combination with standard of care [5]. The first analysis of HRQOL by Fizazi et al [26] used the FACT-P score to address general HRQOL. Hereby, data of 674 patients in the enzalutamide arm and 264 patients in the placebo arm were accessible. The authors found a significant HRQOL benefit of the combination with enzalutamide, which was observed for the total FACT-P score (net differences −1.5 [enzalutamide] vs −13.7 [placebo], $p < 0.001$) as well as other subdomains of the FACT-P questionnaire. As expected, baseline FACT-P total scores were lower than those observed in the nmCRPC setting [21,22]. Subsequent additional HRQOL analyses confirmed the positive effect on HRQOL in the enzalutamide subgroup [27].

The PREVAIL trial included 1717 patients with chemotherapy-naïve mCRPC who were randomized to receive either enzalutamide 160 mg/d or placebo. HRQOL was assessed with the EQ-5D (-3L) questionnaire, and completion rates exceeded 90% at all time points. The authors found a significantly smaller decline in general HRQOL based on the EQ-5D visual analog scale (−1.3 [enzalutamide] vs −4.4 [placebo], $p < 0.0001$) in favor of enzalutamide. Similarly, numerous subscales at various time points favored enzalutamide [28]. As shown in Fig. 2, both AFFIRM and PREVAIL have a low risk of bias.

The ALSYMPCA trial included patients with mCRPC without visceral metastases, who had received chemotherapy, or

Table 3 – Main features of studies addressing patients with metastatic castration-resistant prostate cancer.

Study	Intervention	Phase	*n*	Follow-up	Tool	HRQOL baseline	Main findings
Harland et al (2013) [24] (COU-AA-301)	ABI + ADT vs PBO + ADT	III	1395	Median 20.2 mo	FACT-P	NR	Significant improvements in FACT-P total scores in 48% (ABI) vs 32% (PBO), $p < 0.0001$; median time to deterioration in Fact-P total score 59.9 wk (ABI) vs 36.1 wk (PBO), $p < 0.0001$
Basch et al (2013) [25] (COU-AA-302)	ABI + ADT vs PBO + ADT	III	1088	Median 22.2 mo	FACT-P	FACT-P (total): ABI: 122 PBO: 123	Median time to deterioration in FACT-P total scores: 12.7 mo (ABI) vs 8.3 mo (PBO), $p = 0.003$; median time to deterioration in FACT prostate cancer subscale: 11.1 mo (ABI) vs 5.8 (PBO), $p < 0.0001$
Fizazi et al (2014) [26] (AFFIRM)	ENZA vs PBO	III	938	Up to 25 wk	FACT-P	FACT-P (total): ENZA: 109 PBO: 111	Net differences in FACT-P total scores: −1.5 (ENZA) vs −13.7 (PBO), $p < 0.001$; ENZA favored in all subscales at week 25
Nilsson (2015) [29] (ALSYMPCA)	RA223 vs PBO	III	921	Up to 44 wk	FACT-P EQ-5D (−5 L)	FACT-P (total): RA223: 104 PBO: 104 EQ-5D (utility): RA223: 0.66 PBO: 0.66	Net differences in FACT-P total scores: −4.8 (RA223) vs −8.7 (PBO), $p = 0.004$; 24.6% (RA223) vs 16.1% (PBO) with meaningful improvement in FACT-P total score, $p = 0.020$; net differences in EQ-5D utility scores: −0.10 (RA223) vs −0.16 (PBO), $p = 0.002$; 29.2% (RA223) vs 18.5% (PBO) with meaningful improvement in EQ-5D utility score, $p = 0.004$
Devlin et al (2017) [28] (PREVAIL)	ENZA vs PBO	III	1717	Up to 61 wk	EQ-5D (−3 L)	EQ-5D (VAS): ENZA: 77 PBO: 76	Net differences in EQ-5D VAS scores: −1.3 (ENZA) vs −4.4 (PBO), $p < 0.0001$; ENZA favored in pain/discomfort subscale up to week 37
Unger et al (2017) [30] (SWOG S0421)	DOC + ATR vs DOC + PBO	III	978	Up to 37 wk	FACT-P QLQ-C30 (GLH)	FACT-P (total): DOC + ATR: 107 DOC + PBO: 107 QLQ-C30 GLH: DOC + ATR: 64 DOC + PBO: 64	No statistically significant differences in QLQ-C30 and FACT-P total score; improved functional status for DOC + ATR ($p = 0.02$)
Eisenberger et al (2017) [32] (PROSELICA)	CAB20 vs CAB25	III	1200	NR	FACT-P	NR	No significant differences in time to deterioration for all FACT-P subscales
Oudard et al (2017) [33] FIRSTANA	CAB20 vs CAB25 vs DOC	III	1168	NR	FACT-P	NR	Longer median time to deterioration in physical well-being for CAB20 vs DOC (14.9 vs 11.3 mo, HR 0.76, 95% CI 0.61–0.94, $p = 0.013$); no differences in remaining subscales
Thiery-Vuillemin et al (2019) [34] (AQUARiUS)	ABI + ADT vs ENZA + ADT	IV	105	12 wk	QLQ-C30	NR.	Net differences in QLQ-C30 GLH scores between ABI and ENZA after 3 mo: 7.05, $p = 0.224$, favors ABI over ENZA; clinically meaningful deterioration of cognitive functioning in 8.0% (ABI) vs ENZA (37.8%), $p = 0.022$

ABI = abiraterone acetate; ADT = androgen deprivation therapy; ATR = atrasentan; CAB20 = cabazitaxel 20 mg/m^2; CAB25 = cabazitaxel 25 mg/m^2; CI = confidence interval; DOC = docetaxel; ENZA = enzalutamide; FACT-P = Functional Assessment of Cancer Therapy-Prostate; GLH = global health status; HR = hazard ratio; HRQOL = health-related quality of life; NR = not reported; PBO = placebo; QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; RA223 = radium-223; VAS = visual analog scale.

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were ineligible or unwilling to receive chemotherapy, were randomized to receive either treatment with radium-223 or placebo in combination with best standard of care [6]. Nilsson [29] reported HRQOL outcomes of 921 patients who were included in the study. The baseline responder rate was >93%. To assess general HRQOL, the FACT-P and the EQ-5D (-5L) questionnaires were used. Hereby, the authors found significantly smaller net differences in FACT-P total scores (−4.8 [radium-223] vs −8.7 [placebo], $p = 0.004$). The proportion of patients with clinically meaningful improvement in FACT-P total score was 24.6% versus 16.1% in favor of radium-223 ($p = 0.020$). Similar results were found for the EQ-5D utility score ($p = 0.004$). Notably, baseline FACT-P total scores were slightly lower than the baseline values reported in the SWOG S0421 [30] and AFFIRM [26] trials. As shown in Fig. 2, the risk of bias was considered to be mostly low.

Unger et al [30] analyzed the HRQOL outcomes of the SWOG S0421 trial [31] that tested the effect of addition of endothelin receptor antagonist atrasentan to docetaxel versus docetaxel monotherapy in symptomatic mCRPC patients. Hereby, 978 patients were randomized, and general HRQOL was assessed using the FACT-P total score as well as the QLQ-C30 global health status. Analogous to the oncological data, no differences regarding HRQOL could be detected for the atrasentan and docetaxel monotherapy subgroups, whereas the functional status was slightly higher for the combination subgroup ($p = 0.02$) [30]. As shown in Fig. 2, the risk of bias of the SWOG S0421 trial was low.

Regarding the effect of cabazitaxel in postchemotherapy mCRPC patients, HRQOL outcomes from the PROSELICA trial [32] are available. In total, 1200 patients were randomized and received either cabazitaxel 20 mg/m^2 or cabazitaxel 25 mg/m^2. General HRQOL was assessed by the FACT-P questionnaire. Hereby, no significant differences were detected regarding time to deterioration of the respective FACT-P subscales. The authors did not report baseline values of FACT-P total scores. Since PROSELICA was an open-label study, risk of bias assessment showed mixed results (Fig. 2).

In the FIRSTANA trial, 1168 patients with chemotherapy-naïve mCRPC were randomized into one of the three following arms: cabazitaxel 20 mg/m^2, cabazitaxel 25 mg/m^2, or docetaxel 75 mg/m^2 [33]. Using the FACT-P questionnaire, the authors found a longer median time to deterioration in physical well-being for cabazitaxel 20 mg/m^2 vs docetaxel 75 mg/m^2 (14.9 vs 11.3 mo, HR 0.76, 95% CI 0.61–0.94, $p = 0.013$) with no meaningful differences in the remaining subscales [33]. Analogous to PROSELICA, no baseline FACT-P values were reported and risk of bias assessment showed mixed results (Fig. 2).

In the observational phase IV AQUARiUS study, HRQOL outcomes of 105 patients with mCRPC receiving either enzalutamide 160 mg/d or abiraterone acetate 1000 mg/d (in combination with 5 mg prednisone daily) in routine clinical practice were recently reported [34]. General HRQOL was assessed using the QLQ-C30 questionnaire. With respect to the QLQ-C30 global health status, the authors found a net difference of 7.05 points favoring the abiraterone over the enzalutamide subgroup. Notably, a clinically meaningful deterioration of cognitive functioning was seen in 8.0% in the abiraterone subgroup compared with 37.8% in the enzalutamide subgroup ($p = 0.022$). No baseline global health status scores were reported and, due to the open-label nonrandomized observational study design, risk of bias assessment showed mostly a high risk of bias (Fig. 2).

3.6. Limitations and future perspectives

HRQOL is of paramount importance in decision guiding for patients with advanced PCa. Fortunately, evidence regarding HRQOL outcomes has significantly increased over the past decade, and reporting of PROMs has become mandatory for confirmatory large trials. Thus, there is strong and consistent evidence from several well-designed phase III trials with a low risk of bias. Notably, the current systematic review had rather strict inclusion criteria, and data from 13 phase III and one phase IV trials have been assessed. To date, we did not find a phase II trial that matched our inclusion criteria. However, high-quality post hoc analyses are available from several contemporary phase II trials with a low risk of bias. For instance, Shore et al [35] and Heidenreich et al [36] analyzed HRQOL outcomes of the TERRAIN trial that randomized 375 patients with mCRPC to receive either enzalutamide 160 mg/d or bicalutamide 50 mg/d. Using the FACT-P as well as EQ-5D questionnaires, the authors observed HRQOL benefits for the enzalutamide compared with the bicalutamide subgroup [36]. Khalaf et al [37] assessed the HRQOL of a randomized phase II trial that randomized 202 patients with mCRPC to receive either enzalutamide 160 mg/d or abiraterone 1000 mg/d upon progression and then switch to abiraterone or enzalutamide as second-line treatment, respectively. Using the FACT-P questionnaire, the authors found favorable net differences in FACT-P total scores for the abiraterone compared with the enzalutamide subgroup for patients aged 75 yr or more ($p = 0.003$), but not for patients younger than 75 yr.

After completion of the systematic literature research, an abstract with HRQOL data of the ARAMIS trial has been published at ASCO 2019 [38]. Hereby, 1509 patients with nmCRPC were randomized to receive either darolutamide 600 mg/d or placebo. General HRQOL was measured via QLQ-PR25 at baseline and every 16 wk after study inclusion. Time to HRQOL deterioration was significantly longer for the darolutamide subgroup (25.8 vs 14.8 mo, HR 0.64, 95% CI 0.54–0.76, $p < 0.01$) [38]. Furthermore, an abstract with HRQOL outcomes of a phase II trial investigating the effect of a combination of abiraterone acetate and the poly(ADP-ribose) polymerase inhibitor olaparib compared with placebo and abiraterone acetate in postdocetaxel patients [39] has been published. The authors used the FACT-P questionnaire and found improved FACT-P total scores (defined as an increase of 6 points or more) in 33% in the combination arm versus 28% in the placebo arm (odds ratio [OR] 1.32, 95% CI 0.64–2.87), with an adjusted net difference of −0.60 (olaparib) versus −2.09 (placebo; 95% CI 3.96–6.92) [40]. Finally, HRQOL data from the TITAN trial that compared Apalutamide 240 mg daily to

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placebo in patients with mHNPC. Using the FACT-P and EQ-5D-5L questionnaire, the authors found comparable HRQOL outcomes in both groups with a median time to deterioration based on the FACT-P total score of almost 8.9 months (95% CI 4.70–11.10) in the apalutamide group and 9.2 months (7.39–12.91) in the placebo group (HR 1.02 [95% CI 0.85–1·22]; $p = 0.85$) [41].

Despite the good evidence for HRQOL outcomes of currently used agents in advanced PCa patients, there are still some pitfalls that have to be considered. As indicated above, multiple validated questionnaires assessing different HRQOL subdomains are currently used, and not all of them are PCa specific. In addition, not all studies published baseline values and HRQOL-related endpoints varied between the studies that were included in the current systematic review. Direct and indirect comparisons are further hampered by the fact that clinical meaningfulness of net differences of the respective scores is defined differently among currently available studies. In order to be able to adequately compare the effects of different systematic therapeutic options, investigators should be encouraged to provide baseline values and address net differences as well as time periods until deterioration of a respective subdomain. Ideally, several well-established validated questionnaires such as the FACT-P questionnaire should be used. Future efforts should further focus on increasing the homogeneity of HRQOL measurements between different studies as well as clinical scenarios.

In addition, it has become more and more apparent that, in addition to systemic therapy, patients benefit from a multimodal approach with a special focus on patient care [42]. A recent randomized trial tested the effectiveness of a multimodality supportive care approach and found significantly reduced unmet needs in the intervention group 3 mo after initiation [43]. Recently, a multicenter phase III randomized trial was designed to further evaluate the impact of supervised physical activity on overall survival in patients with mCRPC [44]. Future research should therefore include the interplay of both medicinal and supportive therapy regimens, and its effect on HRQOL outcomes in patients with advanced PCa.

4. Conclusions

In the current systematic review, over 800 articles were screened and 14 articles were included in the quantitative analysis. Based on mostly phase III trials with a low risk of bias, beneficial effects on HRQOL outcomes have been described for abiraterone acetate and docetaxel in the mHNPC setting, for apalutamide and enzalutamide in the nmCRPC setting, and for abiraterone acetate, enzalutamide, and radium-223 in the mCRPC setting. Efforts should be undertaken to optimize comparability between HRQOL outcomes based on different validated questionnaires as well as integration of supportive care regimens.

***Author contributions*:** Alexander Kretschmer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kretschmer, Ploussard, Tilki.
Acquisition of data: Kretschmer, Ploussard, Tilki.
Analysis and interpretation of data: Kretschmer, Ploussard, Tilki.
Drafting of the manuscript: Kretschmer, Ploussard, Tilki.
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References

[1] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[2] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[3] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
[4] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[5] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[6] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.
[7] Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408–18.
[8] Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019;380:1235–46.
[9] Efficace F, Rees J, Fayers P, et al. Overcoming barriers to the implementation of patient-reported outcomes in cancer clinical trials: the PROMOTION Registry. Health Qual Life Outcomes 2014;12:86.
[10] Knoll T, Omar MI, Maclennan S, et al. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: methodology of the European Association of Urology. Eur Urol 2018;73:290–300.
[11] Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ, et al. Measuring quality of life in men with prostate cancer using the Functional Assessment Of Cancer Therapy-Prostate instrument. Urology 1997;50:920–8.
[12] EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
[13] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

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[14] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[15] van Andel G, Bottomley A, Fossa SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008;44:2418–24.
[16] Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314–25.
[17] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.
[18] Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018;19:194–206.
[19] Morgans AK, Chen YH, Sweeney CJ, et al. Quality of life during treatment with chemohormonal therapy: analysis of E3805 chemohormonal androgen ablation randomized trial in prostate cancer. J Clin Oncol 2018;36:1088–95.
[20] Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465–74.
[21] Saad F, Cella D, Basch E, et al. Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:1404–16.
[22] Tombal B, Saad F, Penson D, et al. Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20:556–69.
[23] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
[24] Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. Eur J Cancer 2013;49:3648–57.
[25] Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol 2013;14:1193–9.
[26] Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol 2014;15:1147–56.
[27] Cella D, Ivanescu C, Holmstrom S, et al. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. Ann Oncol 2015;26:179–85.
[28] Devlin N, Herdman M, Pavesi M, et al. Health-related quality of life effects of enzalutamide in patients with metastatic castration-resistant prostate cancer: an in-depth post hoc analysis of EQ-5D data from the PREVAIL trial. Health Qual Life Outcomes 2017;15:130.
[29] Nilsson S. Radium-223 dichloride for the treatment of bone metastatic castration-resistant prostate cancer: an evaluation of its safety. Expert Opin Drug Saf 2015;14:1127–36.
[30] Unger JM, Griffin K, Donaldson GW, et al. Patient-reported outcomes for patients with metastatic castration-resistant prostate cancer receiving docetaxel and atrasentan versus docetaxel and placebo in a randomized phase III clinical trial (SWOG S0421). J Patient Rep Outcomes 2017;2:27.
[31] Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. Lancet Oncol 2013;14:893–900.
[32] Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m(2)) and the currently approved dose (25 mg/m(2)) in postdocetaxel patients with metastatic castration-resistant prostate cancer—PROSELICA. J Clin Oncol 2017;35:3198–206.
[33] Oudard S, Fizazi K, Sengelov L, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III trial—FIRSTANA. J Clin Oncol 2017;35:3189–97.
[34] Thiery-Vuillemin A, Poulsen MH, Lagneau E, et al. Impact of abiraterone acetate plus prednisone or enzalutamide on fatigue and cognition in patients with metastatic castration-resistant prostate cancer: initial results from the observational AQUARiUS study. ESMO Open 2018;3:e000397.
[35] Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016;17:153–63.
[36] Heidenreich A, Chowdhury S, Klotz L, et al. Impact of enzalutamide compared with bicalutamide on quality of life in men with metastatic castration-resistant prostate cancer: additional analyses from the TERRAIN randomised clinical trial. Eur Urol 2017;71:534–42.
[37] Khalaf DJ, Sunderland K, Eigl BJ, et al. Health-related quality of life for abiraterone plus prednisone versus enzalutamide in patients with metastatic castration-resistant prostate cancer: results from a phase II randomized trial. Eur Urol 2019;75:940–7.
[38] Fizazi K, Shore N, Tammela TL, et al. Impact of darolutamide (DARO) on pain and quality of life (QoL) in patients (Pts) with nonmetastatic castrate-resistant prostate cancer (nmCRPC). J Clin Oncol 2019;37 (suppl):5000.
[39] Clarke N, Wiechno PJ, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018;19:975–86.
[40] Clarke N, Thiery-Vuillemin A, Wiechno PJ, et al. Health-related quality of life (HRQoL) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with olaparib in combination with abiraterone. J Clin Oncol 2019;37(7_suppl):234.
[41] Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol 2019;20(11):1518–30, In this issue.
[42] Primeau C, Paterson C, Nabi G. A qualitative study exploring models of supportive care in men and their partners/caregivers affected by metastatic prostate cancer. Oncol Nurs Forum 2017;44:E241–9.
[43] Paterson C, Primeau C, Nabi G. A pilot randomised controlled trial of a multimodal supportive care (ThriverCare) intervention for managing unmet supportive care needs in men with metastatic prostate cancer on hormonal treatment and their partner/caregivers. Eur J Oncol Nurs 2018;37:65–73.
[44] Newton RU, Kenfield SA, Hart NH, et al. Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL-GAP4): a multicentre, randomised, controlled phase III study protocol. BMJ Open 2018;8:e022899.

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