



European Association of Urology



## Review – Prostatic Disease

# A Systematic Review of Patients' Values, Preferences, and Expectations for the Treatment of Metastatic Prostate Cancer

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### Article info

#### Article history:

Accepted October 20, 2021

#### Associate Editor:

Guillaume Ploussard

#### Keywords:

Metastatic prostate cancer  
Metastasis-directed therapy  
Oligometastatic  
Discrete choice experiment  
Choice behaviour  
Cytoreductive  
Stereotactic ablative radiation therapy  
Stereotactic radiotherapy

### Abstract

**Context:** Advances in systemic agents have increased overall survival for men diagnosed with metastatic prostate cancer. Additional cytoreductive prostate treatments and metastasis-directed therapies are under evaluation. These confer toxicity but may offer incremental survival benefits. Thus, an understanding of patients' values and treatment preferences is important for counselling, decision-making, and guideline development.

**Objective:** To perform a systematic review of patients' values, preferences, and expectations regarding treatment of metastatic prostate cancer.

**Evidence acquisition:** The MEDLINE, Embase, and CINAHL databases were systematically searched for qualitative and preference elucidation studies reporting on patients' preferences for treatment of metastatic prostate cancer. Certainty of evidence was assessed using Grading of Recommendation, Assessment, Development and Evaluation (GRADE) or GRADE Confidence in the Evidence from Reviews of Qualitative Research (CERQual). The protocol was registered on PROSPERO as CRD42020201420.

**Evidence synthesis:** A total of 1491 participants from 15 studies met the prespecified eligibility for inclusion. The study designs included were discrete choice experiments ( $n = 5$ ), mixed methods ( $n = 3$ ), and qualitative methods ( $n = 7$ ). Disease states reported per study were: metastatic castration-resistant prostate cancer in nine studies (60.0%), metastatic hormone-sensitive prostate cancer in two studies (13.3%), and a mixed cohort in four studies (26.6%). In quantitative preference

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elicitation studies, patients consistently valued treatment effectiveness and delay in time to symptoms as the two top-ranked treatment attributes (low or very low certainty). Patients were willing to trade off treatment-related toxicity for potential oncological benefits (low certainty). In qualitative studies, thematic analysis revealed cancer progression and/or survival, pain, and fatigue as key components in treatment decisions (low or very low certainty). Patients continue to value oncological benefits in making decisions on treatments under qualitative assessment.

**Conclusions:** There is limited understanding of how patients make treatment and trade-off decisions following a diagnosis of metastatic prostate cancer. For appropriate investment in emerging cytoreductive local tumour and metastasis-directed therapies, we should seek to better understand how this cohort weighs the oncological benefits against the risks.

**Patient summary:** We looked at how men with advanced (metastatic) prostate cancer make treatment decisions. We found that little is known about patients' preferences for current and proposed new treatments. Further studies are required to understand how patients make decisions to help guide the integration of new treatments into the standard of care.

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## 1. Introduction

In contrast to localised prostate cancer, patients with metastatic prostate cancer have distant spread of disease that is not curable [1]. This disease state has primarily been managed using androgen deprivation therapy (ADT) via medical or surgical castration [1]. In isolation, this intervention can lead to disease progression from metastatic hormone-sensitive prostate cancer (mHSPC) to the androgen-independent state of metastatic castration-resistant prostate cancer (mCRPC) within 11–18 mo, limiting overall survival (OS) [2,3].

Recent advances in systemic therapy (eg, docetaxel, abiraterone acetate, enzalutamide, and apalutamide) have resulted in a dramatic improvement in median OS for patients with mHSPC at 4.8 yr [4–7]. To gain a further oncological benefit, there has been a move to explore local cytoreductive treatments of the primary prostate tumour and its metastases in both mHSPC and mCRPC [1,8,9]. Research is particularly focused on patients with a limited number of metastases, or oligometastatic disease [10]. Local prostate interventions include cytoreductive external beam radiotherapy, cytoreductive radical prostatectomy, and cytoreductive minimally invasive ablative therapies [1,11–15]. In addition, metastasis-directed interventions include stereotactic ablative radiation therapy (SABR), lutetium-177 prostate-specific membrane antigen ligands, radium-223, and metastasectomy [8,16,17].

These novel interventions offer significant oncological promise for patients with metastatic prostate cancer [1]. Furthermore, secondary benefits may also arise from the avoidance or delay of second- and third-line systemic agents and their associated toxicity [16,18]. However, each specific treatment is not without its own treatment-related risk (eg, death) and significant side effects may occur (eg, urinary incontinence, fatigue) [18]. Thus, an understanding of patients' values and preferences for management is

important for patient counselling, decision-making, and guideline development.

This systematic review synthesises the evidence from quantitative preference elicitation studies and qualitative studies reporting on patients' values, preferences, and expectations in the treatment of metastatic prostate cancer.

## 2. Evidence acquisition

This prospectively registered (PROSPERO, CRD42020201420) systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [19,20].

### 2.1. Search strategy

A systematic search of the MEDLINE, CINAHL, and Embase databases was carried out, with searches of reference lists of eligible studies to capture additional relevant articles that met our inclusion and exclusion criteria. In brief, the search key terms included “prostate neoplasm/adenocarcinoma” and “metastasis/oligometastasis/advanced/stage IV/metastatic” and “preference elicitation/discrete choice experiment/stated preference/part-worth utility/functional measurement/paired comparison/pairwise choice/conjoint analysis/conjoint measurement/best-worst scale/contingent valuation/standard gable/time-tradeoff/willingness-to-pay/willingness-to-accept”. The detailed search strategy is provided in the [Supplementary material](#). Search results were limited to the English language and from database inception until November 1, 2020. Review articles, letters, and conference abstracts were excluded at this stage.

The titles and abstracts were reviewed independently by three authors (D.B., M.G.G., V.W.) and adjudicated by a fourth author (M.J.C.). The eligibility criteria were then applied. Any disparities that arose were discussed with

the co-authors until agreement was reached. Agreement was verified by a fifth author (H.U.A.) where required. The full text of the remaining articles was reviewed independently by four authors (D.B., M.G.G., V.W., M.J.C.).

## 2.2. Inclusion and exclusion criteria

We included quantitative preference elicitation studies (ie, discrete choice experiments [DCEs], time trade-off [TTO], and standard gamble) and qualitative studies (ie, interviews, focus groups) reporting on patient preferences for the treatment of metastatic prostate cancer. Studies were excluded if they involved (1) nonmetastatic disease or (2) a mixed cohort of disease states (ie, localised and metastatic) or mixed primary cancers if study outcomes were not presented separately by disease state.

## 2.3. Data extraction

The following data were extracted from all the studies included: reference, authors, publishing journal, year of publication, disease state of the patient population, study size, age, study design or methodology, treatment evaluated, main topic in relation to the study purpose, primary results, and conclusions.

## 2.4. Assessment of methodological quality

For quantitative studies, methodological quality was assessed using the Purpose, Respondents, Explanation, Findings, and Significance (PREFS) quality assessment checklist, which was developed to assess the quality of studies in systematic reviews of patient preference literature ([Supplementary Table 1](#)) [21]. For qualitative studies, methodological quality was assessed using the Standards for Reporting Qualitative Research (SRQR) criteria ([Supplementary Table 4](#)) [22].

## 2.5. Risk of bias

For quantitative studies, risk of bias (RoB) was assessed using an RoB tool covering (1) sample selection, (2) response (or attrition) rate, (3) choice and administration of the methodology, (4) outcome (or health state) presentation, and (5) respondent understanding and data analysis ([Supplementary Table 2](#)). In accordance with previous systematic reviews, high RoB was assigned when the measurement instrument was not valid. If the measurement instrument was valid, RoB was designated as low if there were no individual items marked as high RoB and as moderate if not more than two items had moderate RoB [23]. For qualitative studies, RoB was assessed using the SRQR criteria ([Supplementary Table 4](#)) [22]. Studies with a total score of less than 20 were deemed to have high methodological limitation (RoB).

## 2.6. Assessment of certainty of evidence

The certainty of evidence presented was assessed using Grading of Recommendation, Assessment, Development and Evaluation (GRADE) and GRADE Confidence in the Evidence from Reviews of Qualitative Research (CERQual) for quantitative and qualitative studies, respectively [24,25].

## 2.7. Data analysis

A narrative synthesis (quantitative studies) and a thematic analysis (qualitative studies) of the collected data were undertaken with presentation of an interpretation of major findings in the context of the current field [26]. All discrete data points were analysed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). A meta-analysis of quantitative studies was not performed given the heterogeneous pool of study populations, designs, and outcomes reported.

## 3. Evidence synthesis

### 3.1. Quantity of evidence and characteristics of the studies included

Of the 573 articles identified, 15 studies with a total of 1491 participants met the prespecified eligibility for inclusion in this systematic review, as outlined in the PRISMA-P flow diagram ([Fig. 1](#)) [27–41]. The mean number of participants per study was 99 (standard deviation [SD] 117.14). The study designs reported for the articles included were DCEs ( $n = 5$ ), mixed methods ( $n = 3$ ), and qualitative methods ( $n = 7$ ; [Table 1](#)). The mean age reported for participants ranged from 69.1 to 75.4 yr. The disease state of the participants was mCRPC in nine studies (60.0%), mHSPC in two studies (13.3%), and a mixed mCRPC/mHSPC cohort in four studies (26.6%).

Treatments evaluated in the studies included chemotherapy ( $n = 3$ ; 20.0%), abiraterone acetate ( $n = 4$ ; 26.7%), enzalutamide ( $n = 2$ ; 13.3%), radium-223 ( $n = 1$ ; 6.7%), radiotherapy ( $n = 1$ ; 6.7%), any systemic therapy ( $n = 1$ ; 6.7%), any hormonal therapy ( $n = 4$ ; 26.7%), and any bone-targeted agent ( $n = 3$ ; 20.0%). In total, eight out of 15 studies (53.3%) were commercially funded ([Table 1](#)). Author groups from the UK accounted for the largest number of studies (37%; [Supplementary Fig. 1](#)).

### 3.2. Methodological quality and RoB

Methodological validity assessments for each study are listed in [Supplementary Tables 1–4](#). Of the five quantitative studies, four (80%) reported a high response rate, one (20%) tested participant understanding, and all studies analysed the data correctly ([Supplementary Table 2](#)). For the quantitative studies, the mean PREFS quality score was 4 (SD 0). In terms of validity assessment, none of the studies justified their forced-choice study design; three studies (60%) did not report details of their experimental design. All studies piloted the data collection tool with the target population before implementing the main survey. Two (40%) met most of the analysis criteria. The mean SRQR quality score for the qualitative studies was 18.4 (SD 3.4; [Supplementary Table 4](#)). A single quantitative preference study was deemed to have high RoB ( $n = 1$ ; 20%). Five qualitative studies were deemed to have high RoB ( $n = 5$ ; 50%).

### 3.3. Results

#### 3.3.1. Quantitative treatment preference studies

A summary of the demographics and study design of the quantitative preference studies ( $n = 5$ ) is presented in

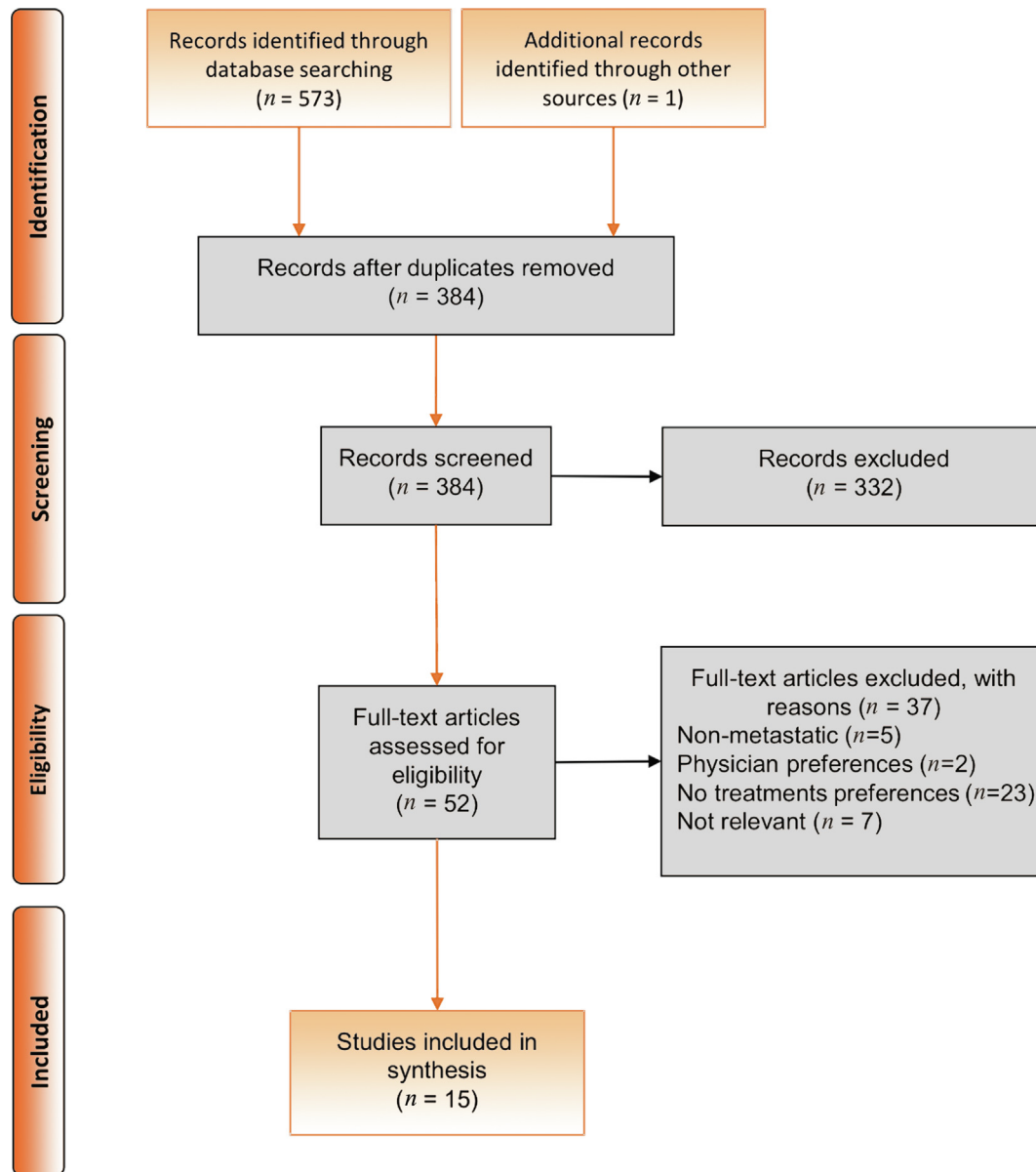


Fig. 1 – Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart.

**Table 1** [27–31]. In all studies, participants were asked to choose between two treatment alternatives and were not given the option to report that they would not be treated. None of the studies justified this study design. The number of treatment attributes evaluated ranged from two to seven (mean 5, SD 2). Overall, treatment effectiveness, delay in time to symptoms, and fatigue emerged as the predominant treatment-related preferences that patients valued (Table 2).

**3.3.1.1. mHSPC.** de Freitas and colleagues [27] explored how 152 patients with mHSPC perceived the risks and benefits of hypothetical abiraterone acetate and docetaxel treatment in three European countries. The study included six treatment attributes: mode of administration, tiredness and fatigue, treatment effectiveness, bone pain, nausea and vomiting, and risk of infection. The authors reported that

treatment effectiveness was the main objective for patients, and that patients wanted to avoid uncontrolled pain. In terms of relative attribute importance (RAI), the treatment attribute ranking was treatment effectiveness (RAI 7.25) followed by pain (RAI 6.26), risk of nausea (RAI 4.12), vomiting (RAI 3.17), risk of fatigue (RAI 2.24), and mode of administration (RAI 2.09) [27].

**3.3.1.2. mCRPC.** In the mCRPC setting, Eliasson and colleagues [28] explored hypothetical treatment options for 285 patients across the UK and Europe. The study included seven treatment attributes: effectiveness (delay in months before chemotherapy), steroid use, possible drug interactions (additional hospital visits for monitoring), cognitive impairment described as “fogginess” (effects on cognition and memory), fatigue, food restrictions, and bone pain. The findings were presented in terms of odds ratios (ORs)

**Table 1** – Characteristics and design of the studies included

No.	Study	Analysis	Design	Setting	Sample size (n)	Mean age, yr (SD)	Disease state	Primary focus	Treatment(s) evaluated	Funding	PREFS/SRQR score
1	de Freitas 2019 [27]	Quantitative	DCE	Hospital	152 (45 <sup>a</sup> )	69.1 (7.7)	mHSPC	Patient perceptions of the risks and benefits of systemic treatments	Docetaxel or AA	C Janssen	PREFS 4
2	Eliasson 2017 [28]	Quantitative	DCE	Hospital	285	70.7 (NR)	mCRPC	Patient perceptions of the risks and benefits of CTx	CTx	C Janssen	PREFS 4
3	Nakayama 2018 [29]	Quantitative	DCE	Hospital	103 (37 <sup>a</sup> )	NR	mCRPC	Investigating the concordance of treatment preferences between patients and physicians	All treatment options	C Janssen	PREFS 4
4	Uemura 2016 [30]	Quantitative	DCE	Hospital	133	75.4 (7.4)	mCRPC	Patient preferences for treatments, subanalysis of symptomatic and asymptomatic patients	Docetaxel, Radium 223, AA	C Bayer Yakuhin	PREFS 4
5	Hauber 2014 [31]	Quantitative	DCE + TTO	Hospital	401	UK: 71.6 (NR) Sweden: 71.5 (NR)	Mixed	Quantify how patients value hypothetical treatments that may delay bone metastasis vs specific bone-targeted treatment risks (eg, ONJ)	Bone-targeted agents	C Amgen	PREFS 4
6	Clark 1997 [32]	Quantitative + qualitative	MMS	Hospital	201	NR	Mixed	Identifying and measuring dimensions of QoL following initiation of treatment for advanced prostate cancer	Hormone therapy	A VA Health Services Research	SRQR 15
7	Ito 2018 [34]	Quantitative + qualitative	MMS	Community	31	NR	mHSPC	Exploring the perspectives of men and carers of men with mHSPC who had received docetaxel	Docetaxel	C Janssen	SRQR 17
8	Clark 2001 [33]	Quantitative + qualitative	MMS	Hospital	201 <sup>b</sup>	NR	Mixed	Understanding patients' experiences of regret regarding their treatment choices and closely examining factors associated with regret	Bone-targeted agents	A VA Health Services Research	SRQR 13
9	Burbridge 2020 [35]	Qualitative	SSI	Hospital	25	72.2 (7.01)	mCRPC	Exploring the symptomatic experience of diagnosis of mCRPC, and the emotional response to this diagnosis	Bone-targeted agent	C Janssen	SRQR 22
10	Catt 2019 [36]	Qualitative	SI	Hospital	37	70.8 (6.81)	mCRPC	Exploring experiences of treatment decisions, information provision, perceived benefits and harms of treatment on patients and partners	Systemic therapy, radiotherapy	A Brighton & Sussex Medical School	SRQR 19
11	Dearden 2019 [37]	Qualitative	SSI	Community	38	NR	mCRPC	Understanding and quantifying the experience of living in patients receiving AA or enzalutamide in pre-CTx and post-CTx settings	AA or enzalutamide	C Janssen	SRQR 14
12	Grunfeld 2012 [38]	Qualitative	SSI	Hospital	21	78 (NR)	Mixed	Interviews exploring the experience and impact of andropause symptoms	Hormone therapy	– Not funded	SRQR 20
13	Iacorossi 2019 [39]	Qualitative	SSI	Hospital	13	NR	mCRPC	Exploring adherence to oral hormone treatment in patients with mCRPC and the factors that may influence adherence	Hormone therapy	– Not funded	SRQR 22
14	Jones 2018 [40]	Qualitative	SSI	Hospital	35	NR	mCRPC	Examining the experiences of patients with advanced prostate cancer and their decision partners	CTx	A NCI + Robert Wood Johnson Foundation	SRQR 22
15	Doveson 2020 [41]	Qualitative	SSI	Hospital	16	NR	mCRPC	Exploring the perspectives of men when facing life-prolonging treatment for mCRPC	CTx, AA, enzalutamide, hormone therapy	A Sophiahemmet Foundation + Kamprad Family Foundation	SRQR 20

NR = not reported; SD = standard deviation; A = academic; C = commercial; M = Mixed; TTO = time trade-off; DCE = discrete choice experiment; MMS = mixed-methods study; SSI = semi-structured interview; SI = structured interview; mHSPC = metastatic hormone-sensitive prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; ONJ = osteonecrosis of the jaw; CTx = chemotherapy; AA = abiraterone acetate; VA = Veterans Affairs; NCI = National Cancer Institute; SRQR = Standards for Reporting Qualitative Research; PREFS = Purpose, Respondents, Explanation, Findings, and Significance for preference and qualitative studies.

<sup>a</sup> Metastatic subgroup cohort.

<sup>b</sup> Clark 1997 [32] & Clark 2001 [33] utilised the same participants.

**Table 2** – Summary of major findings for patient preferences and values in quantitative studies

Patient preference category for values and preferences	Estimates of outcome importance (range across studies)	Participants	Studies	Certainty of evidence	Interpretation of findings
Treatment effectiveness (forced choice)	Two studies ranked treatment effectiveness as the most important attribute ○RAI 7.25 [27] ○RI 32% [29] One study used terminology for treatment impact on overall survival, reporting RI of 19.2% [30]	388	[27,29,30]	⊕⊕○○ Low	Patients consistently consider the effectiveness of a treatment above other treatment-related attributes
Delay in time to symptoms (forced choice/ proportions)	Four studies reported on time to appearance of symptoms: ○One study reported pain as the second most important attribute (RAI 6.26) [27] ○In one study there was a strong preference for treatment that fully controls bone pain (OR 12.069) [28] ○In one study, 80% of the patients would trade at least 3 mo of survival to avoid bone complications [31]	838	[27,28,31]	⊕⊕○○ Low	Patients consistently consider treatment impact on the time until they may develop symptoms of metastatic prostate cancer above other treatment-related attributes
Fatigue (forced choice)	Three studies reported fatigue as a major patient preference: ○Fatigue reported as the most important attribute (RI 24.9%) [30] ○OR 1.365 for treatments that lower the risk of fatigue [28] ○Fourth most important attribute (RAI 3.17) [27]	570	[27,28,30]	⊕○○○ Very low	The relationship between fatigue and treatment choice may be important

RAI = relative attribute importance; RI = relative importance; OR = odds ratio.

and the results suggest that patients prefer treatments that fully control bone pain (OR 12.06, 95% confidence interval [CI] 10.55–13.80) and those that delay chemotherapy (OR 1.72, 95% CI 1.54–1.92). In addition, patients seem to prefer treatments with a lower risk of “fogginess” (OR 2.11, 95% CI 1.84–2.42), a lower risk of fatigue (OR 1.36, 95% CI 1.21–1.52), and fewer additional hospital visits (OR 1.24, 95% CI 1.11–1.39) [28].

The concordance of treatment preferences between patients and physicians in mCRPC was explored in a study of 103 patients in Japan [29]. The study included four attributes: quality of life, effectiveness, side effects, and accessibility. In terms of the relative importance (RI) of attributes, the preference ranking among patients was effectiveness (RI 32%) followed by accessibility of treatment (RI 26%), quality of life (RI 23%), and side effects (RI 19%).

With regard to bone-targeted and systemic agents in the mCRPC setting, Uemura et al [30] explored preferences associated with various treatments (radium-223, abiraterone acetate, and docetaxel) for 133 patients in Japan. The study included six attributes: OS length, time to a symptomatic skeletal event (SSE), administration method, reduction in the risk of bone pain, treatment-associated risk of fatigue, and lost workdays. Patients ranked their preferences as fatigue (RI 24.9%) followed by reduction in the risk of bone pain (RI 23.2%) and OS length (RI 19.2%). The authors compared preferences across symptomatic and asymptomatic patients and found that symptomatic patients placed significantly more importance on delaying an SSE. The authors concluded that patients with CRPC were more concerned about reduced quality of life from side effects of treatment than extension of survival.

Hauber et al [31] explored preferences for bone-targeted agents among 401 patients with mixed disease states in the UK and Sweden. The study used two TTO questions to assess patients’ trade-offs between avoiding metastasis-induced bone complications and longer survival. The results showed that patients were willing to trade up to 5 mo of survival to prevent bone complications.

### 3.3.2. Qualitative studies

A summary of the demographics and study design of the qualitative studies is presented in Table 1 [32–41]. A complete list of all findings by study is available in Supplementary Table 7. Thematic analysis revealed the following key themes: cancer progression and/or survival; pain; fatigue; and other symptoms (sexual dysfunction, bothersome lower urinary tract symptoms [LUTS]; Table 3) [26].

Cancer progression and/or OS benefits related to treatment were a key theme extracted from five of the studies [35–39]. Dearden et al [37] undertook semistructured interviews with 38 patients with mCRPC who were receiving a novel antiandrogen therapy (abiraterone acetate or enzalutamide). Patients were satisfied with these therapies, specifically with reductions in prostate-specific antigen levels and the extended survival quality.

Burbridge et al [35] carried out semistructured interviews with 25 patients diagnosed with mCRPC. Of these patients, 83.3% said they would have taken a medication to delay (metastasis) progression if one had been available, irrespective of side effects. Ito et al [34] conducted semistructured interviews with 31 patients with mHSPC across Europe and the UK who were receiving docetaxel. They found that at the beginning of therapy, men were

**Table 3** – Summary of major findings for patient preferences and values in qualitative studies

Patient preference or value	Key themes defined	Participants	Studies	Confidence of evidence	Interpretation of key themes
Cancer progression or survival	Patients reported that they were willing to accept a range of side effects for potential benefits in cancer progression and/or survival	148	[35–37,39,40]	⊕⊕○○ Low	Patients with metastatic disease may be willing to trade side effects for potential oncological benefits
Fatigue	Fatigue emerged as a prominent treatment-related symptom, significantly impacting patients' QoL	315	[32,34–36,38]	⊕⊕○○ Low	Fatigue has a large impact on QoL for this group of patients and risks for fatigue should be considered in relation to any treatment proposed
Pain	For patients with symptomatic metastatic prostate cancer, pain was consistently the most troublesome symptom	62	[35,36]	⊕○○○ Very low	In symptomatic metastatic disease, avoidance or relief of pain appears to be paramount
Other symptoms: sexual dysfunction, bothersome LUTS	Erectile dysfunction and bothersome LUTS were both frequently reported by patients as negatively impacting their QoL and relationships	263	[32,35,38,41]	⊕○○○ Very low	Local symptoms may have a significant negative impact on patient QoL. Treatments that alleviate local symptoms may lead to secondary benefits

LUTS = lower urinary tract symptoms; QoL = quality of life.

willing to take docetaxel to prolong their life, despite being fearful of the potential side effects and impact on their daily lives.

Fatigue was a key theme related to treatments identified in five of the studies [32,34–36,38]. Catt et al [36] undertook structured interviews with 37 patients with mCRPC, exploring experiences of treatment decisions, perceived benefits and harms of treatment, and the effects on patients' lives. At 3 mo after starting a systemic therapy, 42% of patients said that fatigue was the worst treatment-related side effect. Burbridge et al [35] also found that more than 75% of men with mCRPC reported fatigue or extreme tiredness (*“Whatever [I do] is exhausting”*). In the study by Ito et al [34], fatigue was a significant treatment-related side-effect reported by up to 60.9% of the patients interviewed.

Pain was identified as a theme in two studies [35,36]. Burbridge et al [35] found that pain was one of the most frequent symptoms reported by more than 75% of patients (*“I had a lot of pain”*; *“The pain comes and goes and I usually feel it somewhere in my back”*). Catt et al [36] also found that pain was the worst symptom reported by most patients (46%), although nearly one-fifth (19%) made comments attributing the pain to causes other than prostate cancer (*“I think the pain in my hip could be rheumatic”*; *“My pain in the lower back and shoulder are due to degeneration”*).

Other symptoms related to treatments and local disease were sexual dysfunction and bothersome LUTS, reported in four studies [32,35,38,41]. It is known from earlier work in the era before docetaxel that andropause symptoms (including sexual dysfunction) related to ADT administration were a significant consideration for patients in deciding on whether to commence treatment and a source of treatment regret [32,33,38]. Burbridge et al [35] found that bothersome LUTS were reported by more than 75% of men. Patients were willing to consider supportive treatment to alleviate these symptoms, probably caused by progression of an untreated local tumour.

Grunfeld et al [38] found that most patients reported hot flashes and night sweats, gynaecomastia, cognitive decline, and changes in sexual dysfunction (*“That the erection is rather painful is somewhat of a disincentive to trying it too*

*often”*) as the most frequent adverse effects, affecting everyday functioning. Some patients felt that there was no need for treatment as they were older and single, whereas other reported a belief that the negative aspects outweighed the benefits.

### 3.4. Discussion

#### 3.4.1. Principal findings

This systematic review addresses the evidence from both quantitative and qualitative studies reporting on patients' values, preferences, and expectations in relation to their treatment for metastatic prostate cancer. In quantitative preference elicitation studies, patients consistently valued treatment effectiveness and delay in time to symptoms as the two most highly ranked treatment attributes (low to very low certainty; Table 2). Patients were willing to trade treatment-related toxicity for potential oncological benefits (low certainty). With rapidly emerging local tumour treatments and metastasis-directed therapies now available to patients, these findings are an important consideration for patients and their clinicians.

Qualitative thematic analysis revealed cancer progression or survival, pain, and fatigue as key to treatment decisions (low to very low certainty; Table 3). Patients continue to value oncological benefits in making decisions regarding treatments. However, in the subgroup of symptomatic patients, treatments that could alleviate pain were highly valued even at the expense of survival benefits (very low certainty).

Furthermore, treatment inducing fatigue had a significant negative impact on remaining quality of life (very low certainty). The fact that ionising radiation directed to metastases may secondarily exacerbate or induce fatigue highlights just one example of the difficult decision-making balance that patients and clinicians face [42].

#### 3.4.2. Comparison with prior reviews and guidelines

To the best of our knowledge, this is the first systematic review to evaluate patients' preference and values for treatments following a diagnosis of metastatic prostate cancer.

Prior systematic reviews of patients' preferences involved patients with localised prostate cancer, in which the marginal gains in absolute survival advantage (up to 5% over 10–15 yr) and side effects associated with radical prostate treatment remain the predominant issues [43,44]. In the noncurative setting, it can be assumed that patients' treatment preferences are entirely different.

The landmark STAMPEDE (arm H) study of 2061 men with newly diagnosed metastatic prostate cancer receiving additional local prostate radiotherapy compared to those receiving systemic therapy alone demonstrated a significant OS advantage for patients with low-volume disease in the radiotherapy arm (3-yr OS: 81% vs 73%; hazard ratio 0.68, 95% CI 0.52–0.90;  $p = 0.007$ ) [11].

Against this background, international prostate cancer guidelines have incorporated radiotherapy into the standard of care [45,46]. However, some guidelines recommend dose and fractionation schedules (eg, 36 Gy in 6 fraction) that specifically reduce hospital attendances on the basis that patients would value such an approach in the decision-making process [45]. However, there is no robust evidence detailing how patients balance the risks against the benefits of new treatments applied to this setting to support such a recommendation [18].

#### 3.4.3. Strength and limitations

This is the first study to use an expert panel of urologists, oncologists, and health economists to develop a priori criteria for conducting a systematic review on this topic. This methodological rigour enabled us to summarise the key findings and rate the certainty of the evidence presented using the GRADE and GRADE CERQual criteria, respectively.

Unfortunately, the varied study designs and outcomes reported in the quantitative preference studies precluded a meta-analysis. Furthermore, the diverse qualitative studies reported are likely to reflect the heterogeneous pool of patients included in interviews (varied disease states, metastatic burden, asymptomatic vs symptomatic disease).

Finally, although bone-targeted agents were evaluated in this systematic review, the majority of studies focused on existing systemic therapies. No studies specifically reported on cytoreductive radical prostatectomy, minimally invasive ablative therapies, metastasectomy, or SABR. We are thus unable to report on patient preferences and values with regard to these treatments.

#### 3.4.4. Unanswered questions and future research

This systematic review has predominantly highlighted patient preferences in the context of being offered established systemic therapy options and a limited number of bone-targeted agents. Therefore, our overall understanding of how novel surgical and radiotherapy treatment options are valued by patients remains limited.

However, results support a number of these treatment options continue to be published following robust trial evaluation [8,16,17]. We therefore propose that a reappraisal of patient preferences is now required to permit integration of new treatments into existing standard-of-care pathways. This could take the form of a prospective stand-alone study or indeed could be integrated into ongoing studies during

longitudinal follow-up (eg, NCT01751438, NCT03456843, NCT02454543, NCT03988686, NCT02742675, ISRCTN15704862, NCT03655886, NCT03678025, and NCT03763253).

The IP5-MATTER study (NCT04590976) is a multicentre discrete-choice experiment, currently in its accrual phase, evaluating 300 patients with *de novo* synchronous mHSPC [47]. This trial is designed to evaluate novel treatments (cytoreductive radical prostatectomy, external beam radiotherapy, minimally invasive ablative therapy, and SABR) in addition to systemic therapy for the first time. The study is collecting data on patient characteristics (eg, age, comorbidities) and will offer an insight into whether these also have an impact on patient preferences [48].

It can be hypothesised that the results from studies can then be combined with the effect sizes from future reported interventional randomised trials to determine if, on average, patients are willing to accept the potential effect sizes that are reported in these studies [12,14].

Finally, research on patients' values, preferences, and expectations for treatment should be cognisant of an emerging theme of treatment regret that has been reported for localised disease [49]. One option for mitigating such levels of treatment regret is to assist in the informed decision-making process. It is possible that once novel treatment pathways are established for metastatic prostate cancer, the findings from patient preference elucidation studies (such as DCEs) may be integrated into further work towards the creation of decision treatment aids (DTAs). While residual uncertainty regarding the role of DCEs in the development of such DTAs remains, the methodology is currently being validated in localised prostate cancer and other studies on benign surgical strategies. If proven, this approach may offer utility in the development of any future DTAs for this specific cohort of patients [50–52].

## 4. Conclusions

There is currently limited understanding of patients' preferences for treatment, and thus trade-off decisions, following a new diagnosis of metastatic prostate cancer. For appropriate investment in emerging cytoreductive prostate and metastasis-directed treatment options that are most acceptable to patients, attempts to formalise our understanding of the trade-offs between oncological benefits and risks in this cohort should be performed.

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

*Study concept and design:* Connor, Genie, Burns.

*Acquisition of data:* Connor, Genie.

*Analysis and interpretation of data:* Connor, Genie.

*Drafting of the manuscript:* Connor, Genie.

*Critical revision of the manuscript for important intellectual content:* Connor, Burns, Genie, Bass, Winkler, Khoo, Ahmed, Watson, Dudderidge, Sarwar, Gonzalez, Mangar, Falconer.

*Statistical analysis:* Connor, Genie.



Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Ahmed, Winkler, Khoo, Watson.

Other: None.

**Financial disclosures:** Martin J. Connor 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: Martin J. Connor receives grant funding from the Wellcome Trust and University College London Hospitals Charity. Vincent Khoo is supported by personal fees and nonfinancial support from Accuray, Astellas, Bayer, Janssen, and Boston Scientific. Hashim U. Ahmed is supported by core funding from the UK National Institute of Health Research (NIHR) Imperial Biomedical Research Centre and funding from the Wellcome Trust, Medical Research Council (UK), Prostate Cancer UK, Cancer Research UK, The BMA Foundation, The Urology Foundation, The Imperial Health Charity, Sonacare, Trod Medical, and Sophiris Biocorp for trials and studies in prostate cancer; is a paid medical consultant for Sophiris Biocorp, Sonacare, and BTG/Galil; and is a paid proctor for high-intensity focused ultrasound, cryotherapy, and Rezūm water vapour therapy. The remaining authors have nothing to disclose.

**Funding/Support and role of the sponsor:** None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euros.2021.10.003>.

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