Patients' Preferences for Cytoreductive Treatments in Newly Diagnosed Metastatic Prostate Cancer: The IP5-MATTER Study

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Article info

Abstract

Background and objective: Cytoreductive treatments for patients diagnosed with de novo synchronous metastatic hormone-sensitive prostate cancer (mHSPC) confer incremental survival benefits over systemic therapy, but these may lead to added toxicity and morbidity. Our objective was to determine patients' preferences for, and trade-offs between, additional cytoreductive prostate and metastasis-directed interventions.

Methods: A prospective multicentre discrete choice experiment trial was conducted at 30 hospitals in the UK between December 3, 2020 and January 25, 2023 (NCT04590976). The individuals were eligible for inclusion if they were diagnosed with de novo synchronous mHSPC within 4 mo of commencing androgen deprivation therapy and had performance status 0–2. A discrete choice experiment instrument was developed to elicit patients' preferences for cytoreductive prostate radiotherapy, prostatectomy, prostate ablation, and stereotactic ablative body radiotherapy to metastasis. Patients chose their preferred treatment based on seven attributes. An error-component conditional logit model was used to estimate the preferences for and trade-offs between treatment attributes.

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Key findings and limitations: A total of 352 patients were enrolled, of whom 303 completed the study. The median age was 70 yr (interquartile range [IQR] 64–76) and prostate-specific antigen was 94 ng/ml (IQR 28–370). Metastatic stages were M1a 10.9% (33/303), M1b 79.9% (242/303), and M1c 7.6% (23/303). Patients preferred treatments with longer survival and progression-free periods. Patients were less likely to favour cytoreductive prostatectomy with systemic therapy (Coef. –0.448; [95% confidence interval {CI} –0.60 to –0.29]; $p < 0.001$), unless combined with metastasis-directed therapy. Cytoreductive prostate radiotherapy or ablation with systemic therapy, number of hospital visits, use of a "day-case" procedure, or addition of stereotactic ablative body radiotherapy did not impact treatment choice. Patients were willing to accept an additional cytoreductive treatment with 10 percentage point increases in the risk of urinary incontinence and fatigue to gain 3.4 mo (95% CI 2.8–4.3) and 2.7 mo (95% CI 2.3–3.1) of overall survival, respectively.

Conclusions and clinical implications: Patients are accepting of additional cytoreductive treatments for survival benefit in mHSPC, prioritising preservation of urinary function and avoidance of fatigue.

Patient summary: We performed a large study to ascertain how patients diagnosed with advanced (metastatic) prostate cancer at their first diagnosis made decisions regarding additional available treatments for their prostate and cancer deposits (metastases). Treatments would not provide cure but may reduce cancer burden (cytoreduction), prolong life, and extend time without cancer progression. We reported that most patients were willing to accept additional treatments for survival benefits, in particular treatments that preserved urinary function and reduced fatigue.

1. Introduction

Prostate cancer is the second most common cause of male cancer death worldwide [1]. In the UK, an estimated 12.0% of patients will have de novo synchronous metastatic hormone-sensitive prostate cancer (mHSPC) at index presentation [2]. Recent advances in standard systemic therapy, beyond androgen deprivation therapy (ADT), have improved reported overall survival (OS) from a median of 44–63 mo [3–5].

This has created an oncological "window of opportunity" to explore the benefit of treating the residual primary tumour and established metastases, in an attempt to achieve further disease control [6]. However, we understand very little about patients' preferences and decision-making in relation to the application of novel cytoreductive treatments with noncurative intent that may lead to substantial toxicity and morbidity for this patient group [7].

Preclinically cytoreduction is supported by the premetastatic niche hypothesis, whereby the presence of a persistent primary tumour propagates cancer cell dissemination and may encourage microenvironment changes required for macrometastases [8,9]. Clinical evidence for local cytoreductive treatments is available from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE; Arm-H) randomised study [5,10]. This reported improved OS in a predefined subgroup of patients with low-burden mHSPC following the addition of cytoreductive prostate radiotherapy compared with systemic therapy alone (hazard ratio [HR] = 0.64, 95% confidence interval [CI] 0.52–0.79, $p < 0.001$). Furthermore, a second randomised study in low-volume mHSPC reported improved radiographic

progression-free survival where ADT was combined with either cytoreductive prostate radiotherapy or cytoreductive radical prostatectomy (median follow-up 48 mo, radiographic progression-free survival not reached vs 40 mo, HR 0.43, 95% CI 0.27–0.70, $p = 0.001$) [11]. Other cytoreductive treatments such as cytoreductive prostate ablative therapy (eg, cryotherapy) and metastasis-directed therapy (ie, stereotactic ablative body radiotherapy) have been proposed without current randomised evidence [12,13].

In the Imperial Prostate 5 patients' preferences for additional cytoreductive treatments' discrete choice experiment study (IP5-MATTER), we aimed to ascertain patients' preferences for and trade-offs (survival and side effects) between additional cytoreductive local and metastasis-directed interventions following a diagnosis of de novo synchronous mHSPC.

2. Patients and methods

2.1. Study design

The metastatic prostate cancer patients' attitudes towards treatment of the local tumour and metastasis evaluative research (MATTER) study was a prospective, multicentre, discrete choice experiment patient preference study of 303 patients with de novo synchronous mHSPC in 30 hospitals in the UK [14]. This study included an initial qualitative research phase with patients and health care professionals across our regional cancer network in Northwest London. This study was approved by the UK National Health Research Authority (20/EE/0194) and conducted in accordance with the Good Clinical Practice guidance and the Declaration of Helsinki [15]. This was a joint collaboration between Imperial College London and the Health Economics

Research Unit, University of Aberdeen. This study was funded by the Wellcome Trust (204998/Z/16/Z) and University College London Hospitals Charity (P83624/1348), and was prospectively registered (NCT04590976) and followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines [14,16].

2.2. Study participants

Between December 3, 2020 and January 25, 2023, patients diagnosed with de novo synchronous mHSPC within 4 mo of commencing ADT and having World Health Organization performance status 0–2 were invited to join the study by their treating clinician. Patients who had previously consented to a cytoreductive treatment or developed castrate-resistant disease were excluded. All patients received systemic therapy, which included lifelong gonadotrophin-releasing hormone agonists or antagonists, and bicalutamide. Doublet systemic therapy was determined as per the treating clinician, with reference to current guidelines and local commissioning (eg, docetaxel, enzalutamide, or abiraterone acetate) [17].

2.3. Sample size calculations

Sample size was set at 300 based on the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Conjoint Analysis Task Force recommendations [18]. Using our knowledge of recruitment for our mHSPC treatment randomised study IP2-ATLANTA (NCT03763253) [19], we approximated that recruitment of 300 patients would require 30 sites, recruiting a minimum of ten patients per year with an estimated recruitment rate of 26%. This was comfortably below the 50% recruitment rate observed in similarly designed studies reporting on patients with localised prostate cancer [20].

2.4. Discrete choice experiment instrument

The study protocol has been published previously [14]. A discrete choice experiment was developed to explore patient preferences for additional cytoreductive local and metastasis-directed interventions. In a discrete choice experiment, respondents are asked to make a series of choices. Each choice presents two or more hypothetical treatments, which are described by a set of attributes, for example, risk of urinary incontinence. Across the series of choices, the treatment attributes vary systematically. In each task, respondents are asked to choose the modality of the most preferred treatment. A discrete choice experiment instrument allows researchers to understand how respondents trade off between the treatment attributes. Discrete choice experiments have widely been applied in health care studies [21]. The trade-off in our study was whether patients were willing to accept the likely increased toxicity with additional cytoreductive treatment(s) in exchange for potential survival or cancer progression–free survival benefits.

The discrete choice experiment was developed in line with best practice recommendations [22,23]. The treatment attributes and their associated levels were selected based

Table 1 – Discrete choice experiment attributes, descriptors, and levels included

No.	Attributes	Description	Levels
1.	Treatment modality	How is your metastatic prostate cancer managed?	Hormonal therapies with or without chemotherapy [a] + Followed by a hospital visit every weekday for 4 wk for prostate radiotherapy + Followed by a day-case procedure with recovery time of 2 wk for prostate ablation therapy + Followed by an overnight-stay surgical removal of the prostate with recovery time of 4 wk + Followed by no additional treatment to prostate
2	Specialised radiotherapy	Does the management of your metastatic prostate cancer include specialised radiotherapy to cancer deposits?	Yes, you attend an additional hospital appointment every day for 1 wk No
3	Length of survival after diagnosis	How long a man, on average, is expected to live after the diagnosis?	50, 60, 65, 70 mo
4	Length of time until cancer starts to grow again	How long, on average, until the cancer starts to grow again?	20, 30, 40, 50 mo
5	Risk of urinary incontinence	What is the proportion (%) of men who have permanent urinary incontinence after the treatment?	1% (1/100) 5% (5/100) 10% (5/100) 20% (20/100) 30% (30/100)
6	Risk of erection problem	What is the proportion (%) of men who are not able to maintain an erection sufficient for intercourse?	5% (5/100) 10% (10/100) 20% (20/100) 40% (40/100) 70% (70/100)
7	Risk of extreme tiredness (fatigue)	What is the proportion (%) of men who have extreme tiredness (fatigue) impacting daily activities?	1% (1/100) 10% (10/100) 20% (20/100) 40% (40/100) 60% (60/100)

ADT = androgen deprivation therapy.
[a] Includes ADT with or without docetaxel, abiraterone acetate, enzalutamide, apalutamide, or any other novel antiandrogen.

on a systematic review of patients' values, preferences, and expectations regarding treatment of metastatic prostate cancer [24], and semistructured interviews with patients with advanced prostate cancer and health care professionals (*n* = 20). The treatment options were described by seven attributes: treatment modality, use of specialised radiotherapy, length of survival after diagnosis, length of time until cancer starts to grow again, risk of urinary incontinence,

risk of erection problem, and risk of extreme tiredness (fatigue; Table 1).

All possible combinations of treatment attributes and levels would have resulted in an unfeasibly large number of choices offered to respondents. These were thereby reduced to 36 using a D-efficient experimental design with vague priors for a main-effect only multinomial logit model in NGENE software (version 1.3.0; ChoiceMetrics, Sydney,
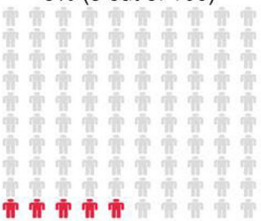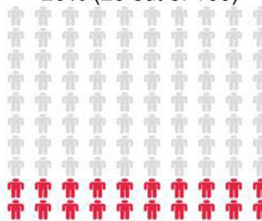
Treatment features	Treatment A	Treatment B
How your metastatic prostate cancer is managed	Hormonal therapies (with or without chemotherapy) followed by **no additional treatment** to prostate	Hormonal therapies (with or without chemotherapy) followed by **an overnight-stay surgery** and **4 wk** of recovery time
Is specialised radiotherapy to cancer deposits included?	No	Yes, there are hospital appointments every day for 1 wk to receive this specialist radiotherapy.
How long a man, on average, is expected to live after the diagnosis?	50 mo	70 mo
How long, on average, until the cancer starts to grow again?	40 mo	60 mo
Proportion of men who have permanent urinary incontinence after treatment (%)	5% (5 out of 100)	20% (20 out of 100)
The proportion of men who are <u>not</u> able to maintain an erection sufficient for intercourse (%)	40% (40 out of 100)	70% (70 out of 100)
The proportion of men who have a feeling of extreme tiredness (fatigue) impacting on daily activities (%)	10% (10 out of 100)	40% (40 out of 100)
Which treatment option would you choose?	☐	☐

Fig. 1 – Example of a discrete choice experiment choice card. Respondents were presented with two treatment options (A or B); both treatment involved systemic therapy. Respondents were asked to "choose" their preference of the two treatments. The risk attributes were presented using icon arrays, ratios, and percentages for ease of comprehension. We split the 36 choices into three blocks of 12 choices to simplify the respondent choices. Further details of the experimental design are available in the Supplementary material.

Table 2 – Baseline characteristics

	Modality	N	Statistic
Age (yr)	Median (IQR)	303	70 (64, 76)
Performance status	0	206	68.0%
	1	88	29.0%
	2	9	3.0%
PSA at diagnosis (ng/ml)	Median (IQR)	303	94 (28, 370)
Gleason grade group/ISUP			
	3 + 3/ISUP 1	0	0%
	3 + 4/ISUP 2	6	2.0%
	4 + 3/ISUP 3	29	9.6%
	4 + 4/3 + 5/5 + 3/ISUP 4	49	16.2%
	4 + 5/5 + 4/5 + 5/ISUP 5	136	44.8%
	Adenocarcinoma with treatment effect	11	3.6%
	No biopsy performed	72	23.8%
TNM staging			
T stage[a]	T2a	13	4.3%
	T2b	3	1.0%
	T2c	10	3.3%
	T3a	60	19.8%
	T3b	110	36.3%
	T4	85	28.1%
	Unknown	22	7.3%
N stage			
	N0	91	30.0%
	N1	198	65.4%
	Unknown	14	4.6%
M stage			
	M1a	33	10.9%
	M1b	242	79.9%
	M1c	23	7.6%
	Unknown	5	1.7%
Metastatic burden			
	High	141	46.5%
	Low	106	35.0%
	Unknown	56	18.5%
IMD decile	1	9	23.0 %
	2	19	6.3%
	3	27	8.9%
	4	34	11.2%
	5	35	11.6%
	6	31	10.2%
	7	34	11.2%
	8	37	12.2%
	9	39	12.9%
	10	37	12.2%
	Unknown	1	0.3%
Planned systemic therapy	ADT	279	92.1%
	Doublet therapy (ADT with chemotherapy or ARSI)	182	60.1%
	Unknown	1	0.33%
Current androgen deprivation therapy	Bicalutamide	87	28.7%
	LHRH agonist	154	50.8%
	LHRH antagonist	62	20.5%
	Maximum androgen blockade	19	6.3%
Current escalated systemic therapy	Enzalutamide	99	32.7%
	Abiraterone acetate	5	1.7%
	Apalutamide	27	8.9%
	Docetaxel	51	16.8%
	None	2	0.7%
	Other	0	0.0%
	Unknown	1	0.3%
Marital status			
	Married	234	77.2%
	Single	9	3.0%
	Divorced	20	6.6%
	Separated	2	0.7%
	Widowed	13	4.3%
	None of the above	4	1.3%
	Prefer not to say	6	2.0%
	Unknown	18	5.9%
Employment status			
	Employee	48	15.8%
	Self-employed/freelance	39	12.9%
	Retired	188	62.1%
	Actively looking for a job	1	0.3%
	Working for own/family's business	7	2.3%
	Unemployed or temporarily laid off	2	0.7%

Table 2 (**continued**)

Modality	N	Statistic
Away from work ill	10	3.3%
Looking after home/family	1	0.3%
Long-term sick/disabled	9	3.0%
Other	4	1.3%
Unknown	17	5.6%

ADT = androgen deprivation therapy; ARSI =androgen receptor signalling inhibitor; IMD = Index of Multiple Deprivation Decile (England and Wales); IQR = interquartile range; ISUP = International Society of Urological Pathology; LHRH = luteinising hormone-releasing hormone; M = metastasis; metastatic burden = metastatic disease as per the CHAARTED definition "high" versus low" (as per Sweeney et al [4]); MRI = magnetic resonance imaging; N = node; PSA = prostate-specific antigen; T = tumour.
  a Clinical T stage was defined on MRI.

NSW, Australia). Details of the experimental design are available in the Supplementary material.

Respondents were presented with two treatment options (A or B); both treatment involved ADT, with or without, androgen receptor signalling inhibitors or chemotherapy. Respondents were asked to "choose" their preference of the two treatments (Fig. 1) [25]. The risk attributes were presented using icon arrays, ratios, and percentages for ease of comprehension. We split the 36 choices into three blocks of 12 choices to minimise the respondent burden. Equal distribution of respondents across the three groupings was monitored prospectively by allocating patients in order of consent.

The preferences were elicited in an electronic discrete choice experiment with three sections. The final instrument also collected information on patients' disease characteristics, demographics, and current treatment. The discrete choice experiment was completed during a routine hospital visit or in the patient's own home using the web-based REDCap platform. All electronic case report forms were completed using deidentified data. Respondents who did not complete any of the discrete choice experiment choices were removed from the analysis.

2.5. Statistical analysis

All analyses were performed using STATA (version 17.0; StataCorp LLC, College Station, TX, USA). Continuous variables were expressed as the median and interquartile range (IQR). Categorical variables were expressed as relative frequencies (percentage), medians, and percentages, as appropriate. Respondents' treatment choices were modelled using an error component logit model.

This models the utility of treatment j in choice t for respondent n as follows:

$$U_{ntj} = \beta X_{ntj} + \varepsilon_{ntj} \tag{1}$$

X_{ntj} is a vector representing the treatment attributes of alternative j presented to patient n in choice t, β is the marginal utility of each attribute, and ε_{ntj} is the error term following a Gumbel distribution. This analysis assumes that patients gain utility (or satisfaction) from treatment, the utility gained depends on the treatment attributes, and respondents choose the treatment that would bring them the highest utility such that

$$U_{ntj} = \beta_0 + \beta_1 MODALITY + \beta_2 RADIOTHERAPY$$
$$+ \beta_3 SURVIVAL + \beta_4 LENGTH + \beta_5 INCONTINENCE$$
$$+ \beta_6 ERECTION + \beta_7 FATIGUE + \gamma_n + \varepsilon_{ntj} \tag{2}$$

$$\gamma_n \, N(0, \sigma)$$

Each patient made 12 choices, and the error term (ε_{ntj}) was likely to be correlated across these choices. We estimate the model with standard errors (SEs) clustered at the individual level. An individual-level error term (γ_n) is used to estimate any individual-specific error (σ).

Here, β_0 represents the treatment option on the left-hand side of the choice set and, if statistically significant, indicated a tendency of patients to select the left-hand treatment option. The interpretation of coefficients depends on the attributes' unit of measurement. The signs (+/–) of the coefficients indicated if a unit change in the attribute increases or decreases the likelihood of choosing a treatment. Further details of model specification are available in the Supplementary material.

From the estimated model results, we estimated how respondents trade off the treatment attributes, which is represented by the ratio of the coefficients. We calculated the incremental treatment benefit in post-treatment OS and progression-free survival that patients are willing to accept in exchange for percentage point increases in the risk of a side effect (Supplementary Table 1). For example, – (β_7/β_3) is the increase in OS time measured in months that would compensate patients for a 1 percentage point increase in the risk of fatigue. To assist the clinical reader in contextualising the results in clinical practice, modalities were combined as "proposed clinical treatment scenarios" of potential side effects and benefits. We constructed six proposed treatment scenarios and estimated the minimum additional survival (months) that a patient would need to gain to be compensated for the treatment burden and side effects of this scenario compared with no additional treatment. We obtain the best estimates of the actual gain that each scenario would offer based on current literature and expert consensus (Supplementary Table 2).

3. Results

3.1. Patient characteristics

Between December 3, 2020 and January 25, 2023, 396 patients with newly diagnosed mHSPC were assessed for eligibility, of whom 352 were recruited and consented to the study (Table 2). Recruitment rate thus exceeded that planned at 88.9% (352/396; Supplementary Fig. 2). Overall, 303 (86.1%; 303/352) patients answered one or more choice

tasks in the survey and 293 (97%; 293/303) patients answered all 12 choice tasks (Supplementary Table 3).

The median age was 70 yr (IQR 64–76) and prostate-specific antigen (PSA) was 94 ng/ml (IQR 28–370; Table 2). Performance status was 0 in 68.0% (206/303), 1 in 29.0% (88/303), and 2 in 3.0% (9/303). A majority of primary tumours were locally advanced—T3a 19.8% (60/303), T3b 36.3% (110/303), and T4 28.1% (85/303), and predominantly of International Society of Urological Pathology (ISUP) grade group 4 (16.2%; 49/303) and 5 (44.8%; 136/303). Nodal stage was N1 in 65.4% (198/303), N0 in 30.0% (91/303), and unknown in 4.6% (14/303). The overall metastatic stages were M1a 10.9% (33/303), M1b 79.9% (242/303), M1c 7.6% (23/303), and unknown in 1.7% (5/303). The metastatic burden as per the CHAARTED criteria was as follows: "high" in 46.5% (141/303), "low" in 35.0% (106/303), and "unknown" in 18.5% (56/303) [26].

All patients received lifelong androgen blockade, with doublet systemic therapy in 60.1% (182/303). Enzalutamide (32.7%; 99/303) and docetaxel (16.8%; 51/303) were used as upfront (immediate) treatments. Utilising the Index of Multiple Deprivation Decile, participants were well represented across all deciles (Table 2).

3.2. Discrete choice experiment model

Table 3 presents the discrete choice experiment results. Compared with no additional treatment, patients chose to avoid surgery requiring an overnight stay in hospital and 4 wk recovery (Coef. [SE] –0.448 [0.080], 95% CI 0.604–0.291, $p < 0.001$)). The radiotherapy regimens that required regular hospital visits for 4 wk or "day case" prostate ablation procedures had no impact on treatment choices (regular hospital visits: Coef. [SE] –0.140 [0.083], 95% CI –0.303 to 0.023, $p = 0.092$; day case procedure: Coef. [SE] 0.028 [0.077]; 95% CI –0.122 to 0.179; $p = 0.710$). The addition of stereotactic ablative body radiotherapy did not impact treatment preference (Coef. [SE] –0.058 [0.048]; 95% CI –0.152 to 0.036; $p = 0.228$). The coefficients for postdiagnosis

increased length of survival and time to cancer progression confirm that patients preferred treatments associated with improved survival and longer progression-free periods ($p < 0.001$; Table 3). When attributes were compared, patients favoured an additional month of gain in survival than a month without cancer progression (Table 3).

Patients preferred a lower probability of developing side effects related to proposed cytoreductive treatments (Table 3). When attributes were compared, a 1 percentage point increase in the risk of urinary incontinence had a larger impact than an equivalent increase in either the risk of fatigue or erectile dysfunction (Table 3).

Figure 2 presents the trade-offs patients were willing to make between benefits and side effects of any proposed cytoreductive treatment in terms of OS and progression-free period. Patients would be willing to accept at 10 percentage point increase in the risk of urinary incontinence if post-treatment survival time increased by 3.4 (95% CI 2.7–4.3) mo or the progression-free period increased by 13.2 (95% CI 9.5–16.9) mo. Similarly, patients would be willing to accept a 10 percentage point increase in the risk of extreme fatigue if OS or the progression-free period increased by 2.7 (95% CI 2.2–3.3) or 10.3 (95% CI 7.6–13.0) mo, respectively. Of note, maintenance of erectile function was not a clinically meaningful trade-off relative to OS and progression-free survival when considering a cytoreductive treatment. These results are also presented in a table format in Supplementary Table 4.

3.3. Proposed clinical treatment scenarios

Utilising the discrete choice experiment results, we were able to calculate differences between the required and actual survival gain for the six proposed clinical treatment scenarios (Fig. 3). All scenarios were acceptable by patients—the actual survival gain is greater than the minimum necessary to compensate patients for the additional burden. The largest difference observed was for surgery combined with stereotactic ablative body radiotherapy

Table 3 – Patients' preferences for cytoreductive treatments[a]

Attribute	Coef.	p value	95% CI
Estimated preferences			
Alternative specific constant (mean)	–0.014	0.750	–0.103, 0.075
Alternative specific constant (SD)	0.370	<0.001	0.235, 0.505
Treatment modality (reference: no additional treatment)			
Hospital visits	–0.140	0.092	–0.303, 0.023
Day case surgery	0.028	0.710	–0.122, 0.179
Overnight hospital stay	–0.448	<0.001	–0.604, –0.291
Additional specialised radiotherapy (reference: no specialised radiotherapy)	–0.058	0.228	–0.152, 0.036
1 mo increase in length of survival	0.072	<0.001	0.064, 0.080
1 mo increase in length of time until cancer grows again	0.019	<0.001	0.014, 0.023
1% increase in risk of urinary incontinence after treatment	–2.469	<0.001	–2.962, –1.976
1% increase in erectile function problem	–0.486	<0.001	–0.701, –0.271
1% increase in the risk of fatigue (extreme tiredness)	–1.947	<0.001	–2.172, –1.723
Model information			
Log likelihood	–2061.8		
McFadden's pseudo-R2	0.169		
Number of observations/choices	3580		
Number of respondents	303		
Number of parameters	10		

CI = confidence interval; Coef. = coefficient; SD = standard deviation.
[a] The insignificant alternative specific constant parameters suggest that left-right (reading) bias is not statistically significant in this sample.
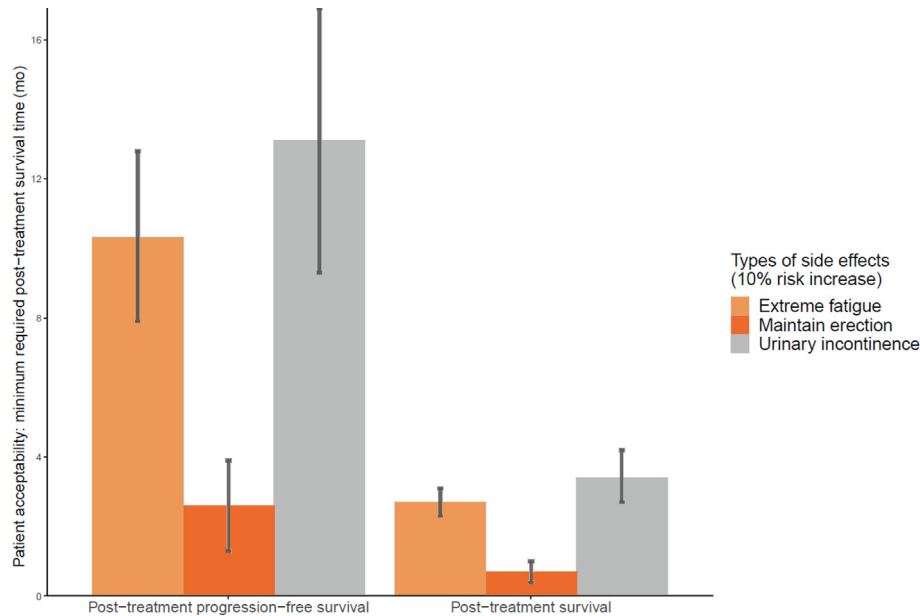
Fig. 2 – Trade-off estimates between cytoreductive treatment benefits and side effects. Error bars denote 95% confidence intervals using the Delta method.
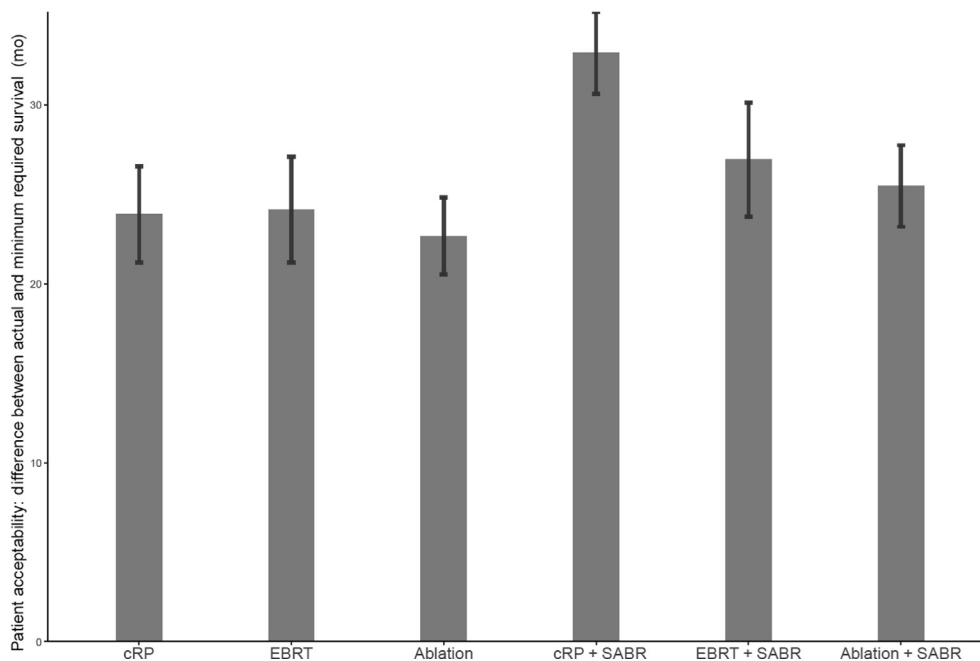
Fig. 3 – Patient acceptability: difference between the actual and minimum level of required survival months needed to switch to a new cytoreductive treatment package. All choices include standard systemic therapy (including docetaxel and novel antiandrogens). See the details in Supplementary Table 2. Error bars denote 95% confidence intervals using the Delta method. Ablation = cytoreductive prostate ablation; cRP = cytoreductive radical prostatectomy; EBRT = cytoreductive external beam radiotherapy; SABR = stereotactic ablative body radiotherapy.

(Fig. 3). This suggests that whilst cytoreductive prostatectomy with systemic therapy alone was not considered acceptable to most patients, when considered as part of the treatment bundle containing stereotactic ablative body radiotherapy (SABR) to metastasis, cytoreductive prostatectomy with systemic therapy would be the most acceptable treatment scenario to patients.

An exploratory latent class analysis was performed, utilising available predictors (ie, performance status, ISUP/Gleason grade group, TNM stage, and metastatic burden), with various latent class models. No significant predictors for class allocation were identified.

Finally, we reported high mean patient satisfaction scores following the completion of our discrete choice

experiment, confirming the acceptability of our discrete choice experiment (Supplementary Table 8).

4. Discussion

In this multicentre discrete choice experiment trial, patients diagnosed with de novo synchronous mHSPC were accepting of additional cytoreductive local and metastasis-directed treatments for potential survival benefits, particularly those that prioritised preservation of urinary function and mitigated fatigue.

To our knowledge, IP5-MATTER is the first study to ascertain patients' preferences and trade-offs for additional cytoreductive treatments in de novo synchronous mHSPC. Previous discrete choice experiments in metastatic prostate cancer have focused on systemic therapy options alone, often in mixed metastatic cohorts [24]. Similar to our findings, they report patients' acceptance to trade off the side-effect risk for potential survival benefit from novel systemic drug therapies [24].

There is growing evidence that decisions made by patients in discrete choice experiments are reflective of real-world health care decisions [27]. A strength of our study is that participants' baseline characteristics, Gleason/ISUP grade group, tumour and nodal staging, PSA, and metastatic burden were all directly comparable with those reported in the STAMPEDE (Arm-H) randomised study that confirmed the benefit of cytoreductive prostate radiotherapy [5,10]. Thus, our study results suggest that the 21.9-mo median survival benefit (63.6 vs 85.5 mo; standard of care [SOC] vs SOC with cytoreductive radiotherapy in low burden) and an adverse event profile for cytoreductive prostate radiotherapy (eg, 7% [44/601] need for urinary catheter) are likely to be accepted by most patients [5,10].

Discrete choice experiments assessing patients' perspectives play an important role in regulatory approval of new treatments and health technologies [28–30]. The US Food and Drug Administration guidance cites discrete choice experiments as its favoured stated preference elicitation approach [28]. Following the STAMPEDE (Arm-H) study, regulatory approval for additional cytoreductive prostate radiotherapy was agreed in Europe, but approval remains elusive elsewhere [10,31,32]. Our study provides additional information to promote the commissioning of cytoreductive radiotherapy. Although some countries favour a dose/fractionation schedule (ie, 36 Gy in six consecutive weekly fractions of 6 Gy) due to fewer hospital visits, with a specific focus on patients highly valuing this cytoreductive treatment attribute, this is not supported by our study findings [32]. Current trials are evaluating the role of additional pelvic nodal radiotherapy and SABR in this cohort, which if proven would lead to a substantial burden of hospital visits [33,34]. Most patients are likely to be accepting of longer dose/fractionation radiotherapy schedules with additional stereotactic ablative body radiotherapy, which would require a greater number of hospital visits for a potential OS benefit based on our findings.

Our study findings can also be utilised by regulators alongside the effect sizes due to be reported in on-going multimodal cytoreductive treatment trials, which combine surgery, ablation, and/or stereotactic ablative radiotherapy (eg, IP2-ATLANTA and SWOG 1802) [33,34]. The risk of fatigue from the addition of stereotactic ablative radiotherapy to oligometastases is reported to be between +4% and +9%, and the risk of urinary incontinence related to cytoreductive radical prostatectomy is between +8% and +16% in published randomised studies [11,35–38]. Our results suggest that given these rates of urinary incontinence and fatigue, most patients would consider accepting cytoreductive surgery only where it were combined with stereotactic ablative body radiotherapy and where such a combination reported a minimum additional absolute OS benefit of 4 mo.

Finally, this study should be viewed within the context of the increasingly important theme of regret from prostate cancer treatment emerging in the localised disease setting [39]. An option to overcome this and improve decisional conflict is to provide high-quality decision treatment aids consistent with patients' informed values, which form part of the shared decision-making process [40,41]. There is growing evidence that discrete choice experiments can be embedded as a method of providing a value-centric choice for patients [42–44]. It is possible to utilise our study findings with future proposed multimodal cytoreductive treatment pathways to create a highly effective decision treatment aid.

Our study is not exempt from limitations. To minimise patient burden, we were unable to offer a wide range of treatment choices such as surgical metastasectomy, radioligand therapies (eg, lutetium-177 [177Lu]-PSMA-617) or escalated triplet systemic therapy, which are emerging in mHSPC [45–47]. Similarly, to minimise patient burden, we were unable to consider all possible attributes relevant to patients' decision-making and did not include opt-out options. Finally, our study was conducted in the UK, and the results are most applicable to this group of patients.

5. Conclusions

Patients diagnosed with de novo synchronous mHSPC are accepting of additional local and metastasis-directed cytoreductive treatments for potential survival benefits, particularly those that prioritise preservation of urinary function and mitigate fatigue.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.06.010.

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