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Evaluating the trade-offs men with localised prostate cancer make between the risks and benefits of treatments: the COMPARE study

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TITLE: Evaluating the trade-offs men with localised prostate cancer make between the risks and benefits of treatments: the COMPARE study

RUNNING TITLE: Trade-offs between risks and benefits for treating prostate cancer

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Abstract

Purpose: COMPARE (COMparing treatment options for ProstAte cancer) aimed to evaluate and quantify the trade-offs patients make between different aspects of active surveillance and definitive therapy.

Methods: A Discrete Choice Experiment (DCE) tool was used to elicit patients' preferences for different treatment characteristics in 34 urology departments. Patients with localised prostate cancer completed the DCE within one week of being diagnosed and before they made treatment decisions. The DCE was pre-tested (N=5) and piloted (n=106) with patients. Patients chose their preferred treatment profile based on six characteristics: *treatment type* (active surveillance, focal therapy, radical therapy), *return to normal activities*, *erectile function*, *urinary function*, *not needing more cancer treatment* and *10-15 year cancer-specific survival*. Different tools were designed for low-intermediate (n=468) and high-risk (n=166) patients. An error-components conditional logit model was used to estimate preferences and trade-offs between treatment characteristics.

Results: Low-intermediate risk patients were willing to trade 6.99% absolute decrease in survival to have active surveillance over definitive therapy. They were willing to trade 0.75%, 0.46% and 0.19% absolute decrease in survival for a one-month reduction in time-to-return to normal activities, and 1% absolute improvements in urinary and sexual function, respectively. High-risk patients were willing to trade 3.10%, 1.04% and 0.41% absolute decrease in survival for a one-month reduction in time-to-return to normal activities and 1% absolute improvements in urinary and sexual function, respectively.

Conclusions: Patients with low-intermediate risk prostate cancer preferred active surveillance to definitive therapy. Patients of all risks were willing to trade-off cancer-specific survival for improved quality-of-life.

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Introduction

Patients with localised prostate cancer have a choice between active surveillance or definitive therapy. Definitive therapy involves a variety of treatment options that range from radiotherapy to surgery that treats the entire prostate and recently, focal therapy. The prostate cancer-specific survival difference between active surveillance and radical therapy is small [1,2,3], whilst side-effects such as incontinence and erectile dysfunction can be significant. The side-effect profile resulting from focal therapy is low with ongoing uncertainty about cancer control [4,5,6].

Whilst it is known that patients decide between treatment options by weighing up the strengths and weaknesses of each, the exact extent to which patients make trade-offs between aspects of treatment and prioritise one aspect of treatment over another is little understood [7]. In particular, the degree to which patients trade-off survival and treatment-related side-effects is not known, though physician opinion plays a large part [8,9,10].

We aimed to evaluate how newly diagnosed patients make treatment choices using a Discrete Choice Experiment (DCE). DCEs are a widely applied preference elicitation method, which assume that patients' value different therapies based on the therapy's characteristics [11,12]. Patients are asked to make hypothetical choices of their most preferred therapy from which patients' treatment preferences can be estimated as well as the trade-offs they make between treatment characteristics.

METHODS

Study design and participants

COMPARE (COMparing treatment options for ProstAte cancer) involved a DCE tool to elicit localised prostate cancer patients' preferences in 34 urology departments (11th/September/2013-28th/July/2015) [Supplement1], within one week of being diagnosed and prior to any treatment decision.

The therapy characteristics and corresponding levels were selected using a sequential process [13,14,15]. First, we used a literature review and expert panel to select characteristics and levels that apply to active surveillance, radical surgery and focal therapy. This led to long list of eight characteristics that were included in a draft DCE survey and tested in semi-structured interviews with five patients [16] [Supplement2]. After three patient interviews no new issues with the survey were identified. Second, based on the interviews, we changed the set of therapy characteristics and levels. We made four changes: we removed characteristics or levels that were not seem appropriate; we added characteristics or levels that were important to patients; we improved our descriptions of risk; and we simplified the complex treatment information. The survey was pilot tested with patients who completed the DCE in their own time and returned it within a sealed envelope. Before the main stage of data collection further minor modifications were made to the survey.

The therapies were described by six characteristics: *treatment type* (active surveillance, radical surgery, focal therapy); *proportion not needing more cancer treatment*; *time to return to normal activities*; *proportion able to maintain an erection*; *proportion with no incontinence* and *proportion surviving cancer 10-15 years* (Table 1). High-risk patients would not be recommended active surveillance and it would be inappropriate to ask them to choose therapies in which the *treatment type* was active surveillance. Therefore, we created two versions of the DCE. Both versions have the

same six characteristics. The DCE version for low-intermediate risk patients describes *treatment type* with three levels: active surveillance, radical surgery and focal therapy. The DCE version for high risk patients describes *treatment type* with two levels: radical surgery and focal therapy. The National Comprehensive Cancer Network (NCCN version 3.2012) risk classification was used. To increase the realism of the treatment profiles we constrained the characteristic levels that could be combined with *treatment type* of active surveillance so that there was no delay in *returning to normal activities*, and no additional *loss of erectile or urinary function* beyond age-related deteriorations.

Based on the characteristics and levels there were 2,064 and 2,048 possible therapy combinations for the low-intermediate and high-risk patients, respectively. An efficient experimental design was used to reduce these to 32 and 48 choice-sets, respectively [17]. Each choice set included two therapy profiles that vary in the six characteristics (Figure 1). We minimised patient burden by reducing the number of choice-sets presented to eight by splitting the choice-sets across four versions for low-intermediate risk and six versions for high-risk. Equal distribution of respondents across the survey versions was prospectively monitored by allocating patients in order of consent.

In the DCE tasks, men were asked to choose between two hypothetical treatment profiles, A and B. The DCE tasks were included in a self-administered paper survey with three sections. Section 1 described the treatment characteristics. Section 2 asked respondents to complete the DCE tasks and state how difficult they were. Section 3 collected socioeconomic characteristics and patient reported outcome measures. Research ethics committee approval was provided by the National Research Ethics Service (Wandsworth) on 5th/March/2012 [Supplement3, Supplement4].

Sample size

The minimum sample that was required to estimate *p* within a percent of the true value with a probability of *α* or greater is given by:

$$n \geq \frac{q}{rpa^2}\Phi^{-1}\left(\frac{1+\alpha}{2}\right)$$

Where Φ-1 is the inverse of the cumulative normal distribution function. To be conservative we calculated the sample size on the assumption that p=0.10, i.e. 10% of patients were likely to prefer one profile in the DCE to another. Each patient completed 8 choices (r=8). Thus, to estimate *p* within 10% of the true value with a probability of 95%, the sample size required was 432 or greater.

Statistical analysis

The DCE data was analysed using multinomial logit regression techniques. In each choice tasks, *r*, each patient, *n* chooses between two treatment profiles, *j*. We assumed patients chose the profile that provided them with the highest utility (or satisfaction) in terms of benefits and harms. The utility a patient obtained from treatment (U_{nrj}) was a linear additive function of the treatment's characteristics and a random error term ε_{nrj}

$$U_{nri} = \alpha_0 + \beta_1 \text{Treatment type} + \beta_2 \text{MoreTreatment} + \beta_3 \text{Activities} + \beta_4 \text{Erection} + \beta_5 \text{Incontinence} + \beta_6 \text{Survival} + \gamma_n + \varepsilon_{ntj} \quad (1)$$

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

The α_0 represents the treatment profile on the left-hand side of the choice set and is statistically significant would indicate a tendency of patients to select the left-hand profile. The interpretation of coefficients depends on the characteristics' unit of measurement, and the interpretation of β_1 depends on the risk group. For low-intermediate risk patients, β_1 represents the preference for active surveillance compared to either focal or radical therapy. For high risk patients, β_1 represents

the preference for focal compared to radical therapy. β_2 represents how a 1 percentage point, or a 1% absolute increase in risk of not needing more cancer treatment in the 10-15 years after treatment affects the probability of choosing a treatment. β_3 represents how a one month increase in time until the patients is able to return to day-to-day activities after treatment affects treatment choice. β_4 and β_5 represent the effect of a 1 percentage point increase in risk of experiencing erectile and urinary function problems on treatment choice, respectively. B_6 represents the effect of a 1 percentage point increase in the probability that patients will survive 10-15 years after treatment on treatment choice. The signs (+/–) of the coefficients indicates if a unit change in the characteristic increases or decreases the likelihood of choosing a treatment. Each patient made eight choices and the error term (ε_{nti}) was likely to be correlated across these choices. We use an error-component specification of the choice model that consists in adding an individual-level error term (γ_n) to the model. This estimated error component represented any individual-specific error (σ). In the DCE literature this type of model is often referred as error component logit (ECL) model. In the multi-level modelling literature, it would be referred as a random intercept logit model.

From the model results, we calculated the trade-offs patients were willing to make between treatment characteristics. These are represented by the ratio of the coefficients. We calculated the percentage point change in survival probability patients are willing to forgo to obtain a one percentage point improvement in another characteristic. For example ($\beta_14/-\beta_16$) is the percentage point decrease in survival that patients are willing to accept to decrease their risk of erectile function problems by one percentage point. Confidence intervals for the survival trade-offs were estimated using the delta method [18].

RESULTS

Patient demographics

106 and 544 were recruited in the pilot and main study, respectively. There were very few changes to the survey after the pilot, therefore we include all data in the analysis. Of those patients who returned the survey, 16 (12 low-intermediate and 4 high-risk) did not complete the DCE. Mean age was 67 years (Table 2). There were 480 (73.8%) patients with low-intermediate and 170 (26.2%) with high-risk disease. Within risk strata, patients were equally distributed over the different survey versions.

Choice model

Patients who completed less than 4 choice sets were excluded from the analysis (29 low-intermediate risk and 8 high-risk) leaving 614 patients. Table 3 presents the regression coefficients and statistical significance. For both groups, α_0 was not statistically significant. Most treatment characteristics were statistically significant. Low-intermediate risk patients preferred *treatment type* of active surveillance to definitive therapy even when the level of other characteristics was controlled for. High-risk patients did not have a statistically significant preference between focal and radical treatment. The negative and statistically significant coefficient for *time-to-return to normal activities* shows patients prefer treatments that allow them to return to their normal activities sooner. The positive and statistically significant coefficients for *not needing more cancer treatment*, *erectile function*, *continence* and *survival* show that patients prefer treatments with higher proportions of patients not needing more treatment, being able to maintain an erection, who do not have incontinence, and survive 10-15 years after treatment.

The coefficients for the 'not needing more treatment', 'erection', 'incontinence' and 'survival' characteristics are for one percentage point increase in probability and can be directly compared to

form a ranking of these characteristics. For both low-intermediate and high-risk patients the order of importance of these characteristics to patients is *survival*, *incontinence*, *not needing more treatment* and *erectile function*.

Marginal rate of substitution (MRS)

Figure 2 presents the trade-offs that patients were willing to make between absolute percentage point changes cancer-specific survival and one unit improvements in the other treatment characteristics. Low-intermediate risk patients were willing to trade, on average, 6.99% absolute cancer-specific survival to have active surveillance rather than focal or radical therapy (Table 3). Low-intermediate risk patients were willing trade 0.75%, 0.46% and 0.19% absolute cancer-specific survival for a one-month reduction in *time to return to normal activities*, and for 1% absolute improvements in *urinary and erectile function*, respectively. Further, if the chance of needing more cancer treatment increased by one percentage point then patients would need to be compensated by an increased chance of cancer survival of 0.36% to make the treatment options equally desirable.

Similarly, high-risk patients were willing to trade 3.10%, 1.04% and 0.41% absolute cancer-specific survival for a one-month reduction in *time to return to normal activities*, and for 1% absolute improvements in urinary and sexual function, respectively. Similarly, if the chance of needing more cancer treatment increased by 1% then patients would need to be compensated by an increased chance of cancer survival of 0.49% to make the treatment option equally desirable.

Both patient groups were willing to forgo more percentage points of cancer-specific survival to obtain an improvement in *urinary function* than in *erectile function* – we interpret this as meaning that patients valued improved *urinary func*tion more highly than improved *erectile function*. High-risk patients were willing to forgo more percentage points of *cancer-specific survival* for improvements in each of the characteristics than low-intermediate risk patients.

DISCUSSION

Our DCE assessed the trade-offs that patients with localised prostate cancer might typically make when able to choose between radical prostatectomy and tissue-preserving strategies (active surveillance and focal therapy). We have shown that patients were willing to forgo survival for earlier return to normal activity, and lower likelihoods of urinary and erectile side-effects.

There are some limitations. First, to minimize the patient burden we limited the number of different treatment types considered and did not include radiotherapy. This may be relevant considering data from ProTect showed a different genito-urinary side-effect profile to prostatectomy [19]. Second, and again to minimize the patient burden, we were unable to consider all possible characteristics, which might also include loss of ejaculation and reductions in penile length. Third, a DCE is a simulation so patients may choose differently when making their actual decision although evidence shows that choices made in DCEs are reflective of actual choices [20]. Fourth, patients in the study were all of a similar age. It is possible that younger and older patients may make different trade-offs between treatment benefits and side effects.

Three previous DCE studies investigated trade-offs in the context of prostate cancer treatment. King *et al* conducted a DCE in 357 patients who were prostate cancer recurrence-free 3 years after being treated and 65 age-matched non-cancer controls [21] and showed a median of 2.5 and 4.0 months survival benefit was needed to offset severe erectile dysfunction and severe loss of libido, respectively, whilst mild and severe urinary leakage needed 4.2 and 27.7 extra months of survival benefit, respectively. Sculpher *et al* conducted a single-centre study of patients with locally advanced prostate cancer [22], and found patients were willing to give up 3 months life expectancy to avoid limitations in physical energy, but least willing to trade life expectancy to avoid hormone

treatment-related hot flushes. Similarly, Eliasson *et al* found patients with metastatic prostate cancer were also willing to trade-off between side effects and treatment efficacy [23]. Other approaches to elicit patient preferences have been used [24,25]. Sommers *et al* used a time trade-off approach in 156 patients with prostate cancer [26], finding patients willing to make trade-offs between quantity and quality-of-life, as well as among different side-effects, especially in older patients with low-risk cancer. Singer *et al* [27] reported 68% of males were willing to accept a 10% reduction in 5-year survival to preserve erectile function.

Getting some insight into the way patients make decisions particularly in relation to the kind of trade-offs they might be willing to make can help in the process of shared decision making and informed consent. If we were to consider only the survival trade-offs patients in our study might make for genitourinary function with the known differences between active surveillance and definitive therapy, low-intermediate risk patients might be willing to accept a total survival detriment of 0.5-9.5%. Similarly, for the known differences in functional outcomes between focal and radical therapy, patients might be willing to accept a survival detriment of 1.8-14.5%. Although these factors are not considered in isolation, the survival detriments that patients might be willing to accept match the maximum 5% absolute risk reduction in cancer-specific mortality that radical therapy confers over active monitoring [1,2,3].

Conclusion

Patients with low-intermediate risk prostate cancer preferred active surveillance to definitive therapy. Patients of all risks were willing to trade-off cancer-specific survival for a higher chance of urinary continence and erectile function.

DECLARATION OF INTERESTS

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study was open to recruitment, numbers of men recruited (n) and key contributors from each site are listed in Supplementary 3 attached.

Role of the funding source

The study funder had no role in study design, data collection, analysis and interpretation and writing. The corresponding author had full access to all study data and final responsibility for the decision to submit for publication.

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Table 1: Characteristics and levels included in the discrete choice experiments

Characteristics	Description	Levels
Treatment modality	How localised prostate cancer is managed	Whole-gland radical therapy Focal therapy Active surveillance
Not needing more cancer treatment	The proportion of men who will not need more prostate cancer treatment in the 10-15 years after treatment (%)	50 60 70 80
Return to normal activities	Length of time until someone is physically able to return to day to day activities after treatment	1 week 1 month 3 months 6months
Erectile function	The proportion of men who are physically able to maintain an erection sufficient for intercourse 12 months after treatment (%)	40 60 80 95
Urinary function	The proportion of men who have no incontinence problem 12 months after treatment (%)	80 85 90 95
Cancer specific survival	The proportion of men who will survive prostate cancer at least 10-15 years after treatment (%)	85 90 95 98

Table 2. Characteristics of 634 men participating and returning the DCE

		High risk		Low intermediate risk	
Characteristic	Modality	N	Statistic	N	Statistic
Prostate-Specific Antigen (PSA) score	Median [IQR]	162	8.77 [6.1 ;11.78]	452	6.7 [5.49 ;8.8]
Age (in years)	Median [IQR]	158	69 [63 ;74]	449	68 [62 ;72]
Gleason score	3+3	162	8.60%	452	56.40%
	3+4	162	69.10%	452	36.90%
	4+3	162	22.20%	452	6.60%
Prostate cancer stage	T1			452	1.10%
	T1A			452	0.90%
	T1B			452	0.20%
	T1C	162	4.90%	452	30.30%
	T2	162	16%	452	29.60%
	T2A	162	12.30%	452	23.90%
	T2B	162	17.30%	452	3.30%
	T2C	162	35.20%	452	8%
	T3A	162	14.20%	452	2.70%
Marital status	Civil partnership	161	6.80%	444	3.60%
	Divorced	161	0.60%	444	1.80%
	Married	161	84.50%	444	83.80%
	None of the above	161	0%	444	0.70%
	Separated	161	5%	444	1.60%
	Single	161	2.50%	444	4.30%
	Widowed	161	0.60%	444	4.30%
Education level	A-level	159	18.90%	441	16.30%
	Degree	159	5.70%	441	11.60%
	Higher degree	159	7.50%	441	3.40%
	No qualification	159	28.30%	441	23.60%
	O-level	159	31.40%	441	32.70%
	Professional	159	8.20%	441	12.50%
Ethnic background	Asian Asian British	161	2.50%	447	2.50%
	Black African Caribbean Black British	161	5%	447	3.80%
	Mixed Multiple ethnic group	161	0.60%	447	0.40%
	None of the above	161	1.90%	447	0.70%
	White English Welsh Scottish Northern Irish British	161	90.10%	447	92.60%

Notes: IRQ – Interquartile range

Table 3. Men's preferences for characteristics and cancer-specific survival trade-offs (heteroskedastic error component multinomial logit)

	Low-to-intermediate risk			High risk		
Attribute	MLE (SE)	P-value	95% CI	MLE (SE)	P-value	95% CI
1. Estimated Preferences						
Constant	0.04 (0.04)	0.29	[-0.04 ; 0.12]	0.06 (0.07)	0.37	[-0.07 ; 0.19]
Focal therapy				-0.05 (0.098)	0.65	[-0.24 ; 0.15]
Surveillance	0.40 (0.115)***	< 0.001	[0.18 ; 0.63]			
1% increase in chance of not needing more cancer treatment	-0.04 (0.017)*	0.01	[-0.08 ;-0.01]	-0.17 (0.021)***	< 0.001	[-0.21 ;-0.13]
1-month increase in time-to-return to normal activities	0.02 (0.004)***	< 0.001	[0.01 ; 0.03]	0.02 (0.007)***	< 0.001	[0.01 ; 0.04]
1% increase in chance of maintaining erectile function	0.01 (0.002)***	< 0.001	[0.01 ; 0.02]	0.02 (0.002)***	< 0.001	[0.02 ; 0.03]
1% increase in chance of not having continence issue	0.03 (0.006)***	< 0.001	[0.01 ; 0.04]	0.06 (0.008)***	< 0.001	[0.04 ; 0.07]
1% increase in chance of cancer-specific survival	0.06 (0.008)***	< 0.001	[0.04 ; 0.07]	0.05 (0.015)***	< 0.001	[0.03 ; 0.08]
SD of Indivdiaul-level errors	0 (0.051)	1	[-0.10 ; 0.10]	0 (0.11)	1	[-0.22 ; 0.22]
2. Model information						
# Respondents	452			162		
# Choices	3616			1296		
Log-likelihood	-2182.2			-765		

*** P-value < 0.1%, ** P-value < 1%, * P-value < 5%

MLE: maximum likelihood estimate; SE: standard error; CI: confidence interval

Figure 1: Example choice set for patients with a) low to intermediate risk and b) high risk prostate cancer

a)

Question 1

Type of prostate cancer management	**Focal therapy**	**Surveillance**
Proportion of men who will **not** need more treatment in the next 10-15 years	70 out of 100	70 out of 100
Length of time to day-to-day activities	6 months	0 months
Proportion of men able to maintain an erection	40 out of 100	100 out of 100
Proportion of men who have no incontinence problem	85 out of 100	100 out of 100
Proportion of men who will survive at least 10-15 years	98 out of 100	85 out of 100
Which management option would you choose?	**Focal therapy** ☐	**Surveillance** ☐
*Please insert a **✓** in the box under the management option you would choose.*		

b)

Question 1

Type of prostate cancer management	**Radical therapy**	**Focal therapy**
Proportion of men who will **not** need more treatment in the next 10-15 years	**60** out of 100	**50** out of 100
Length of time to day-to-day activities	**6** months	**3** months
Proportion of men able to maintain an erection	**80** out of 100	**40** out of 100
Proportion of men who have no incontinence problem	**90** out of 100	**80** out of 100
Proportion of men who will survive at least 10-15 years	**95** out of 100	**85** out of 100
Which management option would you choose?	**Radical therapy** ☐	**Focal therapy** ☐
*Please insert a **✓** in the box under the management option you would choose.*		

Figure 2: Trade offs that low-intermediate risk patients and high risk patients are willing to make between absolute percentage point change in cancer-specific survival and other treatment characteristics