

Manuscript Number: ROB-D-14-00984R1

Title: Estimating Preferences for Treatments in Patients with Localized Prostate Cancer

Article Type: Full Length Article

Section/Category: Clinical Investigation - Genitourinary Cancers

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Abstract: Purpose: Studies of patients' preferences for localized prostate cancer treatments have assessed radical prostatectomy and external radiotherapy, but none of them evaluated brachytherapy. The aim of our study was to assess the preferences and willingness to pay of localized prostate cancer patients for radical prostatectomy, external radiotherapy and brachytherapy, and their related urinary, sexual, and bowel side-effects.

Methods: Observational, prospective cohort study with follow-up until five years after treatment. 704 patients with low or intermediate risk localized prostate cancer were consecutively recruited in 2003-2005. The estimation of preferences was conducted using time trade-off, standard gamble, and willingness-to-pay methods. Side-effects were measured with the Expanded Prostate Index Composite (EPIC), a prostate cancer specific questionnaire. Tobit models were constructed to assess the impact of treatment and side-effects on patients' preferences. Propensity score was applied to adjust for treatment selection bias.

Results: Of the 580 patients reporting preferences, 165 were treated with radical prostatectomy, 152 with external radiotherapy and 263 with brachytherapy. Both time trade-off and standard gamble indicated that the preferences of patients treated with brachytherapy were 0.06 utilities higher than those treated with radical prostatectomy ($p=0.01$). Similarly, willingness-to-pay showed a difference of €57/month ($p=0.004$) between these two treatments. Severe urinary incontinence presented an independent impact on the preferences elicited ($p<0.05$), while no significant differences were found by bowel and sexual side-effects.

Conclusions: Our findings indicate that urinary bothers are the side-effects with the highest impact on preferences, and brachytherapy and external radiotherapy are more valued than radical prostatectomy. These time trade-off and standard gamble preferences assessments as well as the willingness-to-pay estimation could be useful to perform respectively cost-utility or cost-benefit analyses, which can guide health policy decisions.

Suggested Reviewers:

Opposed Reviewers:

Editorial Office

International Journal of Radiation Oncology*Biology*Physics

Dear Editor,

We are pleased to submit a revised version of the manuscript entitled “Estimating Preferences for Treatments in Patients with Localized Prostate Cancer” for publication in the *International Journal of Radiation Oncology*Biology*Physics* after having through and addressed all the reviewers’ queries.

We feel that the reviewer’s suggestions have improved the article and we are grateful for the time dedicated to our paper and the positive comments received.

We hope that you will consider our manuscript is now worthy of publication in the *International Journal of Radiation Oncology*Biology*Physics* and we look forward to hearing from you soon.

Sincerely,

Montse Ferrer

POINT BY POINT RESPONSE TO THE REVIEWER'S COMMENTS

Ref.: Ms. No. ROB-D-14-00984

"Estimating Preferences for Treatments in Patients with Localized Prostate Cancer"

Reviewer #1:

Specific comment #1

How original is the information? There are many studies providing time trade-off (TTO) and standard gamble (SG) utilities for localized prostate cancer patients. However, few, if any, include a large number of patients who were treated with brachytherapy, or elicited willingness-to-pay. To that extent, as the authors point out in the Summary and Discussion (page 9, line 16), this paper provides new and original information.

Response: *We are very thankful for the positive appreciation of the reviewer.*

Specific comment #2

Have the findings been put into the context of other studies? The finding that urinary symptoms have lower utilities than bowel symptoms is surprising and this finding is not compared with findings of other studies. Also, many patients probably have more than one side effect but this is not mentioned. Very few patients in the current study have any bowel side effects. Also, many studies have provided utilities for radical prostatectomy and external beam radiation therapy, and for urinary, bowel, and sexual symptoms. These studies are mentioned in the Introduction (page 2, lines 43 to 53) but their findings are not discussed or compared with those of the current study.

Response: *We thank the reviewer for these remarks. Yes, you are right about the co-occurrence of different side effects: 116 presented two side effects (incontinence with sexual dysfunction was the most frequent couple), 51 patients presented three, and 9 patients presented four. We have added a clarification about this point in the methods section. Also, a paragraph has been introduced in the new version of the manuscript to compare our findings with those of the previous studies, focusing on the relationship between utilities and treatment side effects.*

(Methods, page 8, paragraph 2)

"The second models included urinary incontinence, urinary irritative-obstructive, bowel and sexual side effects as explanatory variables to estimate the independent impact of each one by taking into account the side effect co-occurrence in some patients."

(Discussion, page 12, paragraph 2)

We did not find any statistically significant differences in utilities between patients with or without bowel and sexual side effects. In contrast with our results, the few previous studies focusing on the relationship between utilities and treatment side effects showed that not only urinary, but

also bowel and sexual side effects have an impact on preferences (4,6,22). However, most of these studies were cross-sectional (4,22) in design, therefore without a definition of side-effects based on a before-after comparison. This is especially relevant to distinguish the sexual dysfunction associated to the treatment from that related to other causes. In our cohort, 288 patients already presented sexual problems before treatment, which could not be considered side effects. On the other hand, since our evaluation was carried out 5 years after treatment, time could have attenuated the impact of bowel and sexual side effects on patients' preferences.

Specific comment #3

Is the information appropriate for the IJROBP and its audience? Above all, what is the likely impact of this work on the practice of radiation oncology or the understanding of its science? The information is appropriate and useful to the IJROBP and its audience. Specifically, it provides utilities for cost-effectiveness, cost-utility, and cost-benefit analyses, and the authors state this in the last sentence of the paper (Page 12, lines 8 to 10). The need for utilities for such analyses could be mentioned in the Introduction as a reason for this study and its potential importance and impact.

Response: *We thank the reviewer for this suggestion, and the following sentences have been introduced in the new version of the manuscript:*

(Introduction, page 3, paragraph 2)

"Preferences can be expressed quantitatively as a utility, which is a global, composite, preference-based measure of Health-Related Quality of Life. Utilities indicate a preference or desire for a specific health state, and their estimation is necessary to develop an economic evaluation using cost-utility analyses. Utilities are generally scaled ranging from 1 (best health state) to 0 (death)."

(Introduction, page 4, paragraph 2)

"Willingness-to-Pay (WTP) is not considered a preference or utility, but it is useful for cost-benefit analyses, measuring both in monetary units."

Specific comment #4

Study Design: Was the research well designed, thorough, and scholarly? There are, I believe, major problems with the methodologies of the TTO, SG, and WTP as described on pages 5 and 6 and Appendix A. Firstly, the questions for all 3 techniques asked about patients' bothers. For example, the TTO question, on page 5, line 55-59, is "...how many of these remaining (t*) years of life with your current bothers would you be willing to sacrifice in order to live, from now on, without any of these bothers?". The more usual question is "...how many of these remaining (t*) years of life in your current health would you be willing to sacrifice in order to live, from now on,

in perfect health?". The difference is perhaps subtle, but the use of the term "bothers" might cause patients to consider only the negative aspects of their health state. Furthermore, "bothers" already has some preference or valuation attached to it.

The methods used for the interviews, as described in Appendix A, also have problems that would affect the results. The TTO appears to be open-ended. What happens if the patient does not answer the open-ended question? It sounds like the interviewer moves on to the SG, and the TTO is left unanswered. The TTO interview could offer choices, such as, for example, "would you exchange 1 year of your remaining 20 years of life?", and if the patients replies "yes", then "would you exchange 2 years?", etc., until the maximum number of years the patient is willing to trade-off is reached.

In the SG interview, the risk of death is decreased by 10%. For example, the SG1 question asks the patient if he would accept a 50% chance of cure and 50% chance of death, and if this is not accepted, SG2 asks if he would accept a 60% chance of cure and 40% chance of death. There are two problems with this. Firstly, the patient is never offered a chance of cure lower than 50%, or risk of death higher than 50%. This means that a patient's utility can never be less than 0.5. Secondly, if the patient responds 'no' to SG1 and 'yes' to SG2, the instructions are to go to WTP and presumably his SG utility is 0.6. However, he is not offered the chance to say "yes" to a 55% chance of cure and 45% chance of death, so his utility cannot be 0.55. The same can be said for all questions up to SG5 (90% cure). SG6 give a 5% increase in cure, and the chance of cure is only then increased by 1%.

The WTP also offers only large decrements in monthly income if the open-ended questions (WTP1 and WTP2) are not answered.

Response: *We thank the reviewer's remarks, which we have tried to address adequately. First, we agree on the potential problem of using the term 'bothers' instead of 'health' and we have added a comment in the study limitations paragraph. Second, we understand your concern about missing TTO responses, but this was not the case since only 3 patients did not answer the TTO question. Third, we also agree on the problem of large decrements both for the risk of death in SG and for monthly income in WTP and we added a comment in the limitations paragraph. On the other hand, starting SG by 50%/50% offers the greatest uncertainty; we presumed that if a patient does not choose 50% of cure, he would not accept any lower either.*

(Discussion, page 12, paragraph 3)

"Second, some issues related to the questions for assessing preferences, such as the term 'bothers' and the large decrements presented to patients (both for the risk of death in SG, and for monthly income in WTP), could have affected the results. The term 'bothers' was included because it was easier to understand by patients after curative prostate cancer treatment, but using it instead of the most usual term 'health' could have produced an infraestimation of utilities. The large decrements (for example 10% in SG) applied in the design of this survey were needed to optimize the time spent by patients to answer this long telephone interview. "

Specific comment #5

Are the results credible, and do they clearly support the conclusion(s)? In consideration of the comments about the methods, the results are not that credible because we do not know if patients would have provided utilities in-between those offered in the interview.

Response: *We understand the reviewer's concerns. However, as commented in the limitation paragraph of the manuscript's new version (see response to specific comment 4), large decrements could have affected TTO but not SG, and results obtained with both methods are very similar, providing support to their validity.*

(Discussion, page 12, paragraph 3)

"However, both question issues affected equally to the patients regardless of the treatment applied. Furthermore, the consistency between results from TTO and SG provides support to the obtained utilities' validity."

Specific comment #6

Another point concerning results is that the severity of the side effects in Table 4 are the changes in severity from pre-treatment to 5 years post-treatment, not the actual severity. Patients with "slight" side effects include patients with 'small to moderate problem' at 5 years post-treatment (who had 'no relevant problem' pre-treatment), and patients with 'severe problem' at 5 years post-treatment (who had 'small to moderate problem' pre-treatment). The other two side effect groups represent actual 'no side effects' and 'severe side effects' at 5 years post-treatment according to the definitions on page 5, lines 18 to 36.

The conclusions (Eg., Abstract, page 1, line 55, and Discussion, page 9, line 6-8, and page 11, line 59 to page 12, line 5) state that brachytherapy is preferred to radical prostatectomy. While this is true, there are very small differences between external beam radiation therapy and brachytherapy (Table 3), and external beam is also preferred to prostatectomy. The authors do not state this conclusion. And while the Tobit model indicates that only the brachytherapy utilities are statistically significantly different from those for prostatectomy, the actual differences between external beam and brachytherapy coefficients are very small, and the p-values for external beam range from 0.029 to 0.059, and are thus <0.05 or barely above.

Response: *We thank the reviewer for these remarks. To solve them, a figure entitled "Distribution of patients' symptom severity at the end of follow-up according to baseline symptom severity (pre-treatment evaluation)" has been introduced in the new version of the manuscript. Also, we followed your suggestions about the description of external radiotherapy results, and the corresponding sentences have been modified in the abstract and discussion section.*

(Results, page 9, paragraph 2)

“Figure 1 shows the proportion of patients who improved, remained stable, or worsened since baseline (pre-treatment) until the end of follow-up. Considering the patients who had reported no relevant urinary incontinence at baseline, in the surgery group 32% remained stable (white bars), 30% worsened slightly (light red bars), and 38% worsened severely (dark red bars); while >65% of patients remained stable in the external and interstitial radiotherapy groups. More than half of the 50 patients with small-moderate incontinence at baseline did not present deterioration. The graphic showing patients with severe urinary incontinence at baseline was not constructed due to small group size (n=12). Regarding urinary irritative obstructive side effects, most of deteriorations observed were slight, and 73% of patients with severe problems at baseline improved after treatment. Bowel side effects were scarce, especially among surgery patients. Most patients (n=288) presented severe sexual problems before treatment, and a high proportion of those with no relevant or small-moderate problems at baseline presented sexual side effects at the end of follow-up.”

(Discussion, page 11, paragraph 1)

“Regarding external radiotherapy, statistically significant higher utilities than radical prostatectomy were shown by TTO, and p value was only barely above 0.05 for WTP. Previous studies comparing these treatments by using indirect methods reported contradictory results (6,19,22). The small differences between external radiotherapy and brachytherapy coefficients indicate that both are preferred to prostatectomy.”

(Discussion, page 13, paragraph 2)

This study provides preferences and WTP from patients with localized prostate cancer who had been treated with radical prostatectomy, external radiotherapy or brachytherapy after 5 years of follow-up. To our knowledge, this is the first study estimating preferences for brachytherapy, and also one of the few eliciting WTP values from patients with localized prostate cancer. In conclusion, our findings indicated that urinary bothers are the side effects with highest impact on preferences, and brachytherapy and external radiotherapy are more valued than radical prostatectomy.

Specific comment #7

Are the study's limitations discussed? Implications? Some limitations are discussed on page 11, line 16 - 47. The major limitation of the study and the use and applicability of its results are that it was done 5 years after treatment and these "side effects" may not be related at all to the original treatments. The effects of time, especially in this sample of older men, may have caused or worsened these symptoms.

Response: *We thank the reviewer for the remark, and the following sentences have been introduced in the new version of the manuscript*

(Discussion, page 13, paragraph 1)

“Third, preferences were elicited only at 5 years after treatment, and we do not have information about their evolution over time, from short- to long-term follow-up. This cohort (32) showed a stable side effect pattern from second to fifth year, except for a late worsening in incontinence for brachytherapy and in sexual function for external radiotherapy which appeared around the fourth year. However, mechanisms of adaptation to side effects may have affected patients’ preferences producing an infra-estimation of treatment impact.”

Specific comment #8

Writing. There are very few small grammatical errors (eg., the "are" on page 2, line 26 should be "is", the paper generally is well-written.

Response: *We thank the reviewer for this correction, which has been introduced. Furthermore, a review of the English grammar has been performed in the new version of the manuscript:*

(Introduction, page 3, paragraph 3)

“While obtaining utilities by the indirect method with generic questionnaires is easier...”

Specific comment #9

Figures and tables? The tables are adequate and complete.

Response: *We very much appreciate this positive comment by the reviewer.*

Reviewer #2:**General comment**

The authors use 3 different methods to determine patients' preferences for treatment of localized prostate cancer and to quantitative the impact of symptoms on patients' lives after treatment. 580 men with low or intermediate risk prostate cancer from a multi center study on management of localized prostate cancer were included. Treatment choice was determined by discussion between physicians and patients. Quality of life was evaluated prospectively at baseline and annually using EPIC. Side effects at 5 years were rated as none, slight or severe. The impact on quality of life was judged by 3 methods: the standard gamble, time trade off, and willingness to pay. For the most part the methodology is well explained.

Propensity scores were used to balance the cofounders between treatment groups for radical prostatectomy, brachytherapy, and external beam radiation. Not surprisingly, the worse the side effects that were experienced, the more patients would be willing to pay, or risk, in order to live life free of toxicity. Incontinence and severe urinary irritative or obstructive symptoms had the most impact on quality of life. Patients treated by radical prostatectomy fared worse than those treated by either external beam radiation or brachytherapy.

Response: *We very much appreciate the positive comments of the reviewer, and are willing to introduce the modifications suggested (see responses to specific comments).*

Specific comment #1

This is an interesting analysis and a creative means of quantifying how much prostate cancer patients are bothered by the side effects of their treatment. Although for the most part the article is well written and understandable by a non quality of life research expert, some additional explanations would be useful. For example, the use of the word "utilities" as in the introduction, lines 43 and 47, should be defined for the benefit of those readers not familiar with the PORPUS quality of life tool. A definition such as this one taken from the PORPUS web site would be helpful: "Utility is a global, composite, preference- based measure of health-related quality of life. Utility-based measures indicate preference or desire for a health state. Utilities are generally scaled from 0 (dead) to 1(full or perfect health), although negative values can be assigned to health states considered to be worse than death."

Response: *We thank the reviewer for the remark, and the following sentences have been introduced in the new version of the manuscript:*

(Introduction, page 3, paragraph 2)

"Preferences can be expressed quantitatively as a utility, which is a global, composite, preference- based measure of Health-Related Quality of Life. Utilities indicate a preference or desire for a specific health state, and their estimation is necessary to develop an economic evaluation using cost-utility analyses. Utilities are generally scaled ranging from 1 (best health state) to 0 (death)."

Specific comment #2

In addition, the Tobit model should be more clearly explained so the reader can interpret the clinical significance of the various coefficients of the latent variable.

Response: *Following the reviewer's suggestion, the explanation about the Tobit model has been extended in the new manuscript's methods section.*

(Methods, page 8, paragraph 2)

"Tobit models assume there is a latent variable which hypothetically takes values further beyond the extreme point. As our interest lies in the observed variable (utilities) and not in the latent one, coefficients of the Tobit models were transformed from the latent variable into marginal effects on the observed variable. This transformation allows the interpretation of marginal effects as the difference in mean preference values between the correspondent and the reference category using the original utility scale, where 1 is the best health, and 0 death(40)."

Specific comment #3

Finally, the authors should acknowledge that there may be cultural differences that affect the impact of symptoms which might come out in a larger international European cohort.

Response: *We agree with the reviewer's suggestion and the following changes have been introduced in the new version of the manuscript:*

(Discussion, page 13, paragraph 1)

"Fifth, loss to follow-up is also a possible source of bias in longitudinal studies, but the high response rate (90%) obtained minimized it. Finally, our results may have limited generalisability for other countries, as the impact of symptoms in the preferences may be affected by cultural dissimilarities."

Estimating Preferences for Treatments in Patients with Localized Prostate Cancer

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Financial support for this study was provided by Instituto de Salud Carlos III FEDER (FIS PI08/90090); the Catalan Agency for Health Information, Assessment and Quality (grant AATRM 436/05/2008); and a Fundación Carolina Fellowship (2010-2011). The funding agreement ensures the authors' independence in designing the study, interpreting the data, and writing and publishing the report. All authors declared no conflicts of interest.

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Keywords: Prostate cancer, utility assessment, willingness to pay.

Running title: Preferences in Localized Prostate Cancer.

SUMMARY

We estimated preferences and willingness to pay from patients with localized prostate cancer who had been treated with radical prostatectomy, external radiotherapy or brachytherapy after 5 years of follow-up. To our knowledge, this is the first study estimating preferences for brachytherapy, and also one of the few eliciting willingness to pay values for prostate cancer treatments. Preferences elicited by any of the methods showed statistically significant differences among treatments in favour of brachytherapy.

estimation could be useful to perform respectively cost-utility or cost–benefit analyses, which can guide health policy decisions.

INTRODUCTION

Prostate cancer is the most common cancer in men in the United States and the European Union with over 350,000 and 200,000 cases diagnosed annually, respectively (1). Earlier detection related to prostate-specific antigen (PSA) screening is reflected in the diagnosis of younger patients at local stages (2). Patients with localized prostate cancer have the choice of very distinct treatments, such as surgery, radiotherapy, or active surveillance, with substantially different patterns of side-effects (3). This has led to a growing interest in the consideration of Health-Related Quality of Life (HRQoL) and preferences.

Preferences can be expressed quantitatively as a utility, which is a global, composite, preference- based measure of Health-Related Quality of Life. Utilities indicate a preference or desire for a specific health state, and their estimation is necessary to develop an economic evaluation using cost-utility analyses. Utilities are generally scaled ranging from 1 (best health state) to 0 (death). The prostate cancer patients' preferences or utilities can be directly elicited using methods such as standard gamble (SG) and time trade-off (TTO) or indirectly using multiattribute utility instruments (e.g. EQ-5D and Health Utility Index).

While obtaining utilities by the indirect method with generic questionnaires is easier(4), their limitations in estimating prostate cancer patient's preferences have been repeatedly pointed out (5-8) because they do not cover sexual, urinary or bowel dimensions. A systematic review of studies estimating utilities for these patients noted the variability among values for the same health states (9), which arose in part from the differences in elicitation methods, severity and the individuals evaluated (patients themselves, patients' partners, subjects with no prostate cancer or physicians). Studies focusing on actual patients with localized prostate cancer valued descriptive theoretical scenarios (10-18) or patients' own health state (6-8,19-21).

The assessment of utilities after prostate cancer treatment by measuring patients' health states with disease-specific HRQoL instruments has been published along the last decade (4-7,15,19,20,22). Studies evaluating radical prostatectomy (6,19,20,22) and radiation therapy (6,19,22) showed that utilities decreased significantly after both treatments, but none of them evaluated brachytherapy. Research

focusing on the relationship between utilities and treatment side-effects reported small but significant associations with bowel, urinary and sexual functions (4,6,22).

Willingness-to-Pay (WTP) is not considered a preference or utility, but it is useful for cost-benefit analyses, measuring both in monetary units. The monetary valuation of an intervention or health outcome can be made with the contingent valuation method (23,24). The subject is asked to think about the contingency of the existence of a market-place for his health benefit and to state the maximum he would be willing to pay for that benefit (25). Few studies have elicited WTP in prostate cancer patients, most are focused on diagnostic testing (26-28), and there is only a recent one on treatments(29). It showed that patients experiencing moderate to severe declines in urinary and sexual function reported slightly higher WTP values, but without statistically significant differences with respect to stable patients (29).

The aim of our study was to assess the preferences and willingness to pay of localized prostate cancer patients for radical prostatectomy, external radiotherapy and brachytherapy, and their related urinary, sexual, and bowel side-effects.

METHODS

Study Design and Patient Recruitment

This was an observational, prospective study of a localized prostate cancer patient cohort. Patients included in the 'Spanish Multicentric Study of Clinically Localized Prostate Cancer' were enrolled from April 2003 to March 2005 from 10 Spanish hospitals. Details of the study have been described elsewhere (30-32). Briefly, patients newly diagnosed with localized prostate cancer (stages T1 or T2) treated with prostatectomy, external radiotherapy or brachytherapy, and with no previous transurethral prostate resection, were included. Decisions on treatment options were jointly made by patients and physicians. HRQoL evaluations were performed before and annually after treatment.

Questions developed to elicit preferences were introduced at the 5-year follow-up evaluation. Each patient responded to a computer-assisted telephone interview carried out by a single research technician who was specially trained to administer HRQoL and preference questionnaires. Full details of the interview are shown in Appendix A. From the 841 patients recruited, 44 did not meet inclusion criteria, 18 were transferred to other hospitals before treatment, and 14 refused to participate. Of the 765 patients included in the cohort, 61 high-risk patients were excluded, 59 died during the 5 year follow-up, and 65 could not be interviewed or did not complete the direct method preference questions, giving a total of 580 participants for this analysis.

Research protocols were approved by the ethics review board of each participating hospital and written informed consent was required for each participant according to the 2000 revision of the Declaration of Helsinki.

Instruments

Demographic and clinical characteristics at pre-treatment were recorded at clinical sites in the recruitment evaluation and included: age, marital status, social class, PSA, Gleason score, and co-morbidities, among others. Patients were staged (33) through a directed history and physical examination. The definition of D'Amico et al. (34) was used to classify patients into low and intermediate risk groups. A

summary indicator of co-morbidities was derived from a checklist of 12 common chronic conditions to classify patients into three categories (0-1, 2-3, ≥ 4 conditions). Social class was assigned according to the respondent's most recent occupation using an adapted version of the British Registrar General's Social Classes (35).

Side-effects were measured with the Spanish version of the Expanded Prostate Index Composite (EPIC). It contains 50 items with 5-point Likert scales of response to measure bother and function of urinary incontinence, urinary irritative-obstructive, bowel, sexual and hormonal domains (36,37). As previously reported (31), responses to bother items of each domain were considered to classify patients with 'no relevant problem'; 'small to moderate problem' (at least one distressful symptom); and 'severe problem' (at least one very distressful symptom). Pre-treatment and 5 year post-treatment evaluations were considered to define patients as: severe side-effects (change from no relevant to severe problems); slight side-effects (only one level worsening); and no side-effects (patients without worsening).

Time Trade-Off (TTO)

In the TTO method, the person is asked to imagine that he has t years to live (25), and how many of these years (x) he would be willing to sacrifice to achieve perfect health, compared with his current state. The TTO preference is defined as the number of years of life traded divided by the number of years of total remaining life. The quotient (x/t) was then subtracted from one. For example, for a patient with incontinence who is willing to give up 2 years of his 10 years of total remaining life to be continent, the health state incontinence is given a utility value of 0.8 ($1 - [2/10]$). This study used the patient's Spanish age-adjusted life expectancy as the reference duration (t^*)(38) and the main TTO question was: "If your life expectancy today were (t^*) years, how many of these remaining (t^*) years of life with your current bothers would you be willing to sacrifice in order to live, from now on, without any of these bothers?"

Standard Gamble (SG)

In the SG method, a preference value is measured by the choice that a person makes between a certain outcome (to continue living in his current health state) and a gamble with a probability X of living in perfect

health versus a probability $1-X$ of immediate death. The preference value is the indifference point (25). In this study the subjects were asked to imagine that there was a novel cure or treatment for the symptoms resulting from their prostate cancer, the SG question was: "If you chose this treatment, your bothers would either disappear completely, or this new cure or treatment could cause your death. Suppose that from the 100 people that choose the new cure, P people are completely cured (with all bothers related to the prostate disease disappearing completely) and the other $(100-P)$ people die because of this new cure. Would you risk trying this new cure?" The risk of death was varied in intervals of 10% (40% to 10%) and then of 1% (5% to 1%). To compute a patient's preference, the quotient that was equal to the probability of death at the point of indifference was subtracted from one $(1-[100-P]/100)$.

Willingness-to-Pay (WTP)

The subject was asked to imagine that he could get a cure so as not to suffer the bothers of his prostate cancer, it is fully effective and there is not risk if he chooses it, but it is not publicly reimbursed, so he must pay for it. The WTP question was: "Let's imagine that your monthly net income is €1000. So, from this €1000 monthly net income, what amount, at the most, would you be willing to pay per month so as not to suffer from the current bothers caused by your prostate disease?". We considered a standard monthly income of €1000 because this was the most frequent salary in Spain in 2008 (39).

Data Analyses

To account for treatment selection bias, propensity scores were estimated to maximize the balance in the distribution of possible confounders among treatment groups. As described previously (32), a multinomial logistic regression model was constructed to estimate the conditional probability of receiving a treatment (radical prostatectomy, external radiotherapy, or brachytherapy) given measured covariates (prostate cancer characteristics, general health status, and socio-demographic variables). The final multinomial logistic regression model for calculating the propensity scores had c-statistic of 0.92 (95%CI=0.90-0.94) for radical prostatectomy, 0.81 (95%CI=0.78-0.85) for external radiotherapy, and 0.85 (95%CI=0.82-0.88) for brachytherapy, indicating good discriminant ability. The differences among treatment groups were tested using the Chi-squared test for categorical variables or one-way analysis of variance for continuous

variables. To assess whether the propensity score achieved better balance in the covariates, differences on means and percentages by treatment groups after propensity score adjustment were tested using linear or logistic regression models, respectively.

Bivariate comparisons of the preferences and the WTP between groups defined by socio-demographic variables, tumor characteristics, treatment and side-effects were performed using Kruskal Wallis test because of the skewed distribution of dependent variables. We constructed Tobit regression models with TTO, SG and WTP as dependent variables, to assess the preferences according to the 1) treatments; and 2) side-effects. The first models included the treatment as independent variable and were adjusted by propensity scores. The second models included urinary incontinence, urinary irritative-obstructive, bowel and sexual side-effects as explanatory variables to estimate the independent impact of each one by taking into account the side-effect co-occurrence in some patients. These models were also adjusted by variables which showed statistically significant differences in the bivariate analysis. Tobit models assume there is a latent variable which hypothetically takes values further beyond the extreme point. As our interest lies in the observed variable (utilities) and not in the latent one, coefficients of the Tobit models were transformed from the latent variable into marginal effects on the observed variable. This transformation allows the interpretation of marginal effects as the difference in mean preference values between the correspondent and the reference category using the original utility scale, where 1 is the best health, and 0 death(40). Statistical analysis was performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA) and R Statistical Software.

RESULTS

Table 1 shows unadjusted means and percentages along with propensity score adjusted estimates. Of the 580 patients included, 165 were treated with radical prostatectomy, 152 with external radiotherapy, and 263 with brachytherapy. There were statistically significant differences among treatment groups at baseline in several variables (age, social class, tumor characteristics, neoadjuvant hormonal treatment, EPIC urinary incontinence and sexual domains) which disappeared after adjustment by the propensity score.

Figure 1 shows the proportion of patients who improved, remained stable, or worsened since baseline (pre-treatment) until the end of follow-up. Considering the patients who had reported no relevant urinary incontinence at baseline, in the surgery group 32% remained stable (white bars), 30% worsened slightly (light red bars), and 38% worsened severely (dark red bars); while >65% of patients remained stable in the external and interstitial radiotherapy groups. More than half of the 50 patients with small-moderate incontinence at baseline did not present deterioration. The graphic showing patients with severe urinary incontinence at baseline was not constructed due to small group size (n=12). Regarding urinary irritative obstructive side-effects, most of deteriorations observed were slight, and 73% of patients with severe problems at baseline improved after treatment. Bowel side-effects were scarce, especially among surgery patients. Most patients (n=288) presented severe sexual problems before treatment, and a high proportion of those with no relevant or small-moderate problems at baseline presented sexual side-effects at the end of follow-up.

Table 2 shows statistically significant differences in the elicited preferences by age groups, while differences by other social or clinical characteristics were not found. Bivariate analysis showed statistically significant differences by treatment (Table 3) for TTO, SG and WTP. Multivariate Tobit model of TTO showed statistically significant differences for external radiotherapy and brachytherapy compared to radical prostatectomy. In this model, patients treated with radiotherapy (external or brachytherapy) presented higher preferences than those patients who had undergone surgery. Tobit models of SG and WTP showed statistically significant differences only between brachytherapy and radical prostatectomy.

Regardless of the direct method used, the preferences elicited were significantly different according to the severity of both urinary side-effects (incontinence and irritative/obstructive) in the bivariate analysis (Table 4). Tobit models confirmed that incontinence presented a statistically significant and independent impact on the preferences elicited, while significance was marginal for irritative/obstructive symptoms. No differences were found by bowel and sexual side-effects.

DISCUSSION

In this study, preferences elicited by any of the applied direct methods showed statistically significant differences among treatments in favour of brachytherapy, compared with radical prostatectomy, in patients with localized prostate cancer 5 years after treatment. This is the first study comparing preferences for brachytherapy with other treatments. TTO showed that patients who had undergone prostatectomy were willing to give up the highest percentage of their remaining life (5%) to make bothers disappear, while patients treated with brachytherapy were willing to sacrifice 3% ($p < 0.001$). The differences between them was higher after adjusting for propensity score (0.06 instead of 0.02 utilities). Also, the patients with prostatectomy were willing to pay the highest value (€47.67/month) to not suffer bothers, while brachytherapy patients were willing to pay almost €16/month less ($p < 0.001$). After adjusting by propensity score, a difference of €57/month ($p = 0.004$) was estimated between these two treatments. Regarding external radiotherapy, statistically significant higher utilities than radical prostatectomy were shown by TTO, and p value was only barely above 0.05 for WTP. Previous studies comparing these treatments by using indirect methods reported contradictory results (6,19,22). The small differences between external radiotherapy and brachytherapy coefficients indicate that both are preferred to prostatectomy.

The patients without urinary side-effects were willing to give up on 2-3% of their remaining life, while the patients with severe incontinence or irritative/obstructive worsening were willing to sacrifice 5% and 8%, respectively. After adjusting for the other side-effects and age, TTO differences between the two extreme groups were similar: 0.047 ($p = 0.02$) for incontinence and 0.051 ($p = 0.07$) for irritative/obstructive symptoms. Similarly, SG showed that patients without urinary side-effects were indifferent about continuing with their present health status or taking a 1-2% chance of death, on average, while the patients with severe incontinence would have taken a chance of 4%, and those with severe irritative/obstructive symptoms a chance of 5%. SG differences after adjustment were very close to those obtained by TTO. Also, patients presenting severe urinary side-effects were willing to pay more than those without (the difference was €30/month for incontinence and €46/month for irritative/obstructive

symptoms). After adjustment, only the difference in urinary incontinence presented a significant independent effect (€67.5/month $p < 0.001$).

We did not find any statistically significant differences in utilities between patients with or without bowel and sexual side-effects. In contrast with our results, the few previous studies focusing on the relationship between utilities and treatment side-effects showed that not only urinary, but also bowel and sexual side-effects have an impact on preferences (4,6,22). However, most of these studies were cross-sectional (4,22) in design, therefore without a definition of side-effects based on a before-after comparison. This is especially relevant to distinguish the sexual dysfunction associated to the treatment from that related to other causes. In our cohort, 288 patients already presented sexual problems before treatment, which could not be considered side-effects. On the other hand, since our evaluation was carried out 5 years after treatment, time could have attenuated the impact of bowel and sexual side-effects on patients' preferences.

Some limitations of this study should be taken into account. First, the main concern regarding observational studies is confounding by treatment-selection bias (for example, surgery is prescribed to younger patients and brachytherapy to patients of lower risk). Propensity score methods are being widely recommended in observational studies (41-43) to account for treatment-selection bias and, thus, identify the true treatment effects. It is worth pointing out that carrying out randomized clinical trials to compare different treatments presents considerable difficulties in these patients (44,45). Second, some issues related to the questions for assessing preferences, such as the term 'bothers' and the large decrements presented to patients (both for the risk of death in SG, and for monthly income in WTP), could have affected the results. The term 'bothers' was included because it was easier to understand by patients after curative prostate cancer treatment, but using it instead of the most usual term 'health' could have produced an infraestimation of utilities. The large decrements (for example 10% in SG) applied in the design of this survey were needed to optimize the time spent by patients to answer this long telephone interview. However, both question issues affected equally to the patients regardless of the treatment applied. Furthermore, the consistency between results from TTO and SG provides support to the

obtained utilities' validity. Third, preferences were elicited only at 5 years after treatment, and we do not have information about their evolution over time, from short- to long-term follow-up. This cohort (32) showed a stable side-effect pattern from second to fifth year, except for a late worsening in incontinence for brachytherapy and in sexual function for external radiotherapy which appeared around the fourth year. However, mechanisms of adaptation to side-effects may have affected patients' preferences producing an infra-estimation of treatment impact. Fourth, this study was done using computer-assisted telephone interviews. The preference assessment task may have been difficult to understand by the patients because it involves the concepts of probability or trade off years (46). In fact, SG is not used as frequently as other techniques because of concerns over patients understanding the concept of probability (12). However, the interviewer was specially trained to introduce correctly each methodology (survival scenarios for the TTO, the role of uncertainty in SG and the notion of market in WTP). Fifth, loss to follow-up is also a possible source of bias in longitudinal studies, but the high response rate (90%) obtained minimized it. Finally, our results may have limited generalisability for other countries, as the impact of symptoms in the preferences may be affected by cultural dissimilarities.

This study provides preferences and WTP from patients with localized prostate cancer who had been treated with radical prostatectomy, external radiotherapy or brachytherapy after 5 years of follow-up. To our knowledge, this is the first study estimating preferences for brachytherapy, and also one of the few eliciting WTP values from patients with localized prostate cancer. In conclusion, our findings indicated that urinary bothers are the side-effects with highest impact on preferences, and brachytherapy and external radiotherapy are more valued than radical prostatectomy. These TTO and SG preferences assessment, as well as the estimation of WTP, reflect the patients' affectation by the side-effects of different treatments for localized prostate cancer, and they are useful to perform cost-utility or cost-benefit analyses (47), which can guide health policy decisions.

Acknowledgments

Financial support for this study was provided by XX; XX; and a XX. The funding agreement ensures the authors' independence in designing the study, interpreting the data, and writing and publishing the report.

All authors declared no conflicts of interest.

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Figure 1. Distribution of patients' symptom severity at the end of follow-up according to baseline symptom severity (pre-treatment evaluation).

The percentages in the bars represent the proportion of patients reporting problems at the end of follow-up. White bars show stable patients; green bars those who improved from baseline; and light and dark red bars those with slight and severe side-effects.

Table 1. Unadjusted and adjusted descriptive of patient characteristics and quality of life scores before treatment.

Unadjusted Descriptive					Adjusted Descriptive (by Propensity Scores)			
	Radical Prostatectomy	External-Beam Radiotherapy	Brachytherapy	p-value	Radical Prostatectomy	External-Beam Radiotherapy	Brachytherapy	p-value
Participants	165	152	263					
Patients Characteristics								
Age. mean (SD)	64.2 (5.5)	69.9 (5.3)	66.8 (6.4)	< 0.001	67.7 (5.2)	66.9 (5.3)	66.4 (5.3)	0.194
< 65 years	87 (53%)	25 (16.4%)	88 (33.5%)	< 0.001	28.5%	27.4%	28.9%	0.489
65 – 70 years	57 (34.8%)	42 (27.6%)	83 (31.6%)		43.6%	36.5%	40.1%	
≥ 70 years	20 (12.2%)	85 (55.9%)	92 (35%)		27.9%	36.1%	31%	
missing	1 (0.6%)	0 (0%)	0 (0%)					
Marital Status								
Nor partner	13 (11%)	13 (9.5%)	24 (10.2%)	0.922	5.6%	13%	11.2%	0.230
Married or with partner	105 (89%)	124 (90.5%)	211 (89.8%)		94.4%	87%	88.8%	
Social Class								
I-II (Managerial-Free-lance professionals)	11 (9.4%)	28 (20.6%)	60 (25.5%)	0.009	12.5%	22.3%	19.5%	0.201
III (Skilled non-manual occupations)	33 (28.2%)	29 (21.3%)	57 (24.3%)		32.1%	22.2%	23%	
IV-V (Manual workers)	73 (62.4%)	79 (58.1%)	118 (50.2%)		55.4%	55.6%	57.5%	
Comorbidities								
0-1	37 (31.4%)	55 (40.2%)	87 (37.0%)	0.122	30.5%	42.5%	36.6%	0.105
2-3	56 (47.5%)	44 (32.1%)	99 (42.1%)		47.4%	32.3%	42.2%	
≥ 4	25 (21.2%)	38 (27.7%)	49 (20.9%)		22.1%	25.3%	21.2%	
PSA (ng/mL). mean (SD)	7.7 (3)	8.1 (3.2)	6.8 (2.1)	< 0.001	7.6 (2.6)	6.7 (2.7)	6.2 (2.7)	0.484
Gleason score. mean(SD)	6.3 (0.7)	5.8 (1.1)	5.5 (0.9)	< 0.001	5.8 (0.8)	4.9 (0.8)	4.4 (0.8)	0.526
Clinical T Stage. n (%)								
T1	107 (64.8%)	88 (57.9%)	214 (81.4%)	< 0.001	72.1%	74.0%	75.1%	0.365
T2	58 (35.2%)	63 (41.4%)	48 (18.3%)		27.9%	25.1%	24.6%	
Tx	0 (0%)	1 (0.7%)	1 (0.4%)		0%	0.9%	0.2%	
Risk group. n (%)								
Low	74 (44.8%)	86 (56.6%)	236 (89.7%)	<0.001	85.8%	86.6%	86.0%	0.985
Intermediate	91 (55.2%)	66 (43.4%)	27 (10.3%)		14.2%	13.4%	14%	
Neoadjuvant hormonal treatment. n (%)								
No	152 (92.1%)	101 (66.4%)	173 (65.8%)		79.1%	83.5%	84%	0.743
Yes	13 (7.9%)	51 (33.6%)	90 (34.2%)	< 0.001	20.9%	16.5%	16%	
Biochemical Failure								
Yes	38 (23%)	53 (34.9%)	63 (24%)	0.026	14.7%	34.9%	29.7%	0.004
No	127 (77%)	99 (65.1%)	199 (76%)		85.3%	65.1%	70.3%	
Quality of life scores. mean (SD)								
EPIC urinary								
Incontinence	93.3 (16.3)	96.1 (10.4)	96.9 (10)	0.028	92.7 (12)	96.7 (12.2)	97.0 (12.1)	0.075
Irritative /obstructive	93.4 (10.9)	94.8 (11.3)	94.2 (10.9)	0.605	92.3 (11.1)	95.9 (11.2)	94.4 (11.2)	0.140
EPIC bowel	98.0 (3.4)	97.2 (6.6)	97.0 (6.5)	0.382	98.2 (5.9)	97.9 (6)	96.5 (6)	0.088
EPIC sexual	58.8 (23.8)	49.6 (23.9)	49.5 (25.2)	0.002	53.9 (24.6)	51.6 (24.9)	51.6 (24.9)	0.825
EPIC hormonal	93.9 (9.2)	94.2 (9.5)	92.8 (10)	0.348	92.7 (9.7)	94.2 (9.9)	93.6 (9.9)	0.651

Abbreviations: EPIC= Expanded Prostate Cancer Index Composite.
* Chi square test or one-way analysis of variance among the three treatment groups.
†Differences on adjusted means and percentages among treatment groups were tested by linear or logistic regression models (with propensity score), respectively.

Table 2. Preferences and willingness to pay values according to socio-demographic and clinical characteristics.

		Time Trade-Off (TTO)		Standard Gamble (SG)		WTP (€ / month)	
Patient Characteristics		Mean (SD)	p-value*	Mean (SD)	p-value*	Mean (SD)	p-value*
Socio-demographic Characteristics							
Age(years)							
	< 65 years	0.96 (0.14)	0.007	0.98 (0.09)	0.083	52.25 (86.81)	<0.001
	65 – 70 years	0.97 (0.09)		0.98 (0.06)		30.33 (58.00)	
	≥ 70 years	0.98 (0.07)		0.98 (0.09)		24.82 (67.37)	
Marital Status							
	Nor partner	0.99 (0.05)	0.117	0.99 (0.08)	0.033†	31.60 (64.44)	0.681
	Married or with partner	0.97 (0.11)		0.98 (0.08)		36.42 (73.97)	
Social Class							
	I-II (Managerial-Free-lance professionals)	0.97 (0.10)	0.464	0.97 (0.10)	0.595	47.39 (84.79)	0.147
	III (Skilled non-manual occupations)	0.95 (0.14)		0.98 (0.08)		39.12 (68.47)	
	IV-V (Manual workers)	0.98 (0.09)		0.98 (0.07)		30.19 (70.12)	
Clinical Characteristics							
Risk Group							
	Low risk	0.97 (0.10)	0.211	0.98 (0.08)	0.863	37.37 (75.50)	0.933
	Intermediate risk	0.96 (0.12)		0.98 (0.09)		32.93 (67.28)	
Comorbidities							
	0-1	0.97 (0.10)	0.414	0.99 (0.05)	0.382	38.80 (89.56)	0.626
	2-3	0.97 (0.11)		0.98 (0.09)		35.73 (63.13)	
	≥ 4	0.97 (0.11)		0.97 (0.10)		31.70 (59.00)	

Abbreviations: SD= Standard deviation WTP= Willingness to pay.

*Kruskal Wallis to compare preferences scores and willingness to pay values among socio-demographic and clinical variables.

Table 3. Preferences and willingness to pay values according to treatment received.

Bivariate Analysis	Time Trade-Off (TTO)			Standard Gamble (SG)			WTP (€ / month)		
	Mean	(SD)	p-value*	Mean	(SD)	p-value*	Mean	(SD)	p-value*
Radical Prostatectomy	0.95	(0.13)	<0.001	0.98	(0.07)	0.01	47.67	(82.01)	<0.001
External Radiotherapy	0.98	(0.07)		0.98	(0.10)		30	(63.20)	
Brachytherapy	0.97	(0.10)		0.98	(0.08)		32.07	(71.63)	
Tobit Models†	Coefficient latent variable	Marginal effect	p-value	Coefficient latent variable	Marginal effect	p-value	Coefficient latent variable	Marginal effect	p-value
Intercept	1.291	0.319	<0.001	1.318	0.357	<0.001	-31.749	-21.841	0.141
Radical Prostatectomy	ref	ref	ref	ref	ref	ref	ref	ref	ref
External Radiotherapy	0.234	0.058	0.027	0.106	0.029	0.212	-58.296	-40.103	0.059
Brachytherapy	0.249	0.061	0.012	0.215	0.058	0.010	-82.542	-56.783	0.004

Abbreviations: SD= Standard deviation. WTP= Willingness to pay.

*Kruskal Wallis to compare preferences scores and willingness to pay values among the three treatment groups.

†Adjusted by propensity scores.

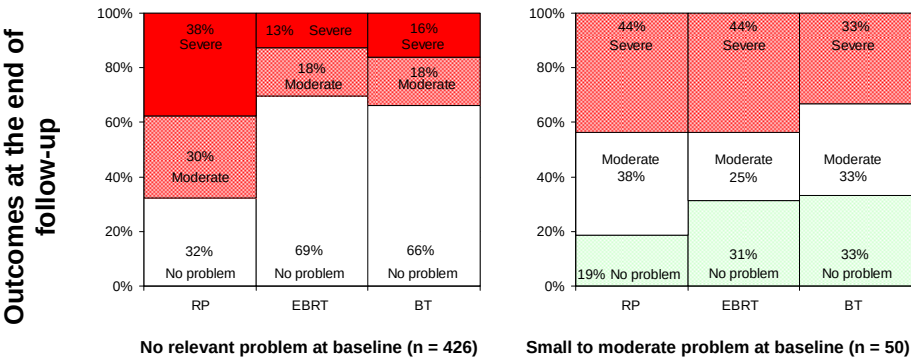
Table 4. Relationship of side effects' severity with preferences and willingness to pay values.

Bivariate Analysis	%	Time Trade-Off (TTO)			Standard Gamble (SG)			WTP (€ / month)		
		Mean	(SD)	p-value*	Mean	(SD)	p-value*	Mean	(SD)	p-value*
EPIC Urinary Incontinence										
No side effects(n=295)	60.5%	0.98	(0.10)	< 0.001	0.98	(0.09)	< 0.001	27.69	(68.51)	< 0.001
Slight side effects(n=108)	22.1%	0.97	(0.12)		1.00	(0.02)		41.85	(75.99)	
Severe side effects(n=85)	17.4%	0.95	(0.10)		0.96	(0.10)		57.24	(80.54)	
EPIC Urinary Irritative/ Obstructive										
No side effects(n=357)	73.2%	0.97	(0.10)	< 0.001	0.99	(0.07)	< 0.001	32.70	(69.19)	0.024
Slight side effects(n=104)	21.3%	0.96	(0.13)		0.97	(0.10)		36.15	(75.30)	
Severe side effects(n=27)	5.5%	0.92	(0.12)		0.95	(0.12)		78.52	(100.75)	
EPIC Bowel										
No side effects(n=391)	80.3%	0.97	(0.11)	0.545	0.98	(0.07)	0.322	35.90	(73.68)	0.232
Slight side effects(n=60)	12.3%	0.97	(0.08)		0.95	(0.14)		47.50	(82.04)	
Severe side effects(n=36)	7.4%	0.98	(0.07)		0.99	(0.04)		18.61	(44.86)	
EPIC Sexual										
No side effects(n=334)	68.4%	0.97	(0.10)	0.179	0.98	(0.09)	0.876	32.56	(70.64)	0.040
Slight side effects(n=101)	20.7%	0.95	(0.14)		0.98	(0.07)		36.93	(70.89)	
Severe side effects(n=53)	10.9%	0.97	(0.08)		0.99	(0.02)		55.66	(89.45)	
Tobit Models		Coefficient latent variable	Marginal effect	p-value	Coefficient latent variable	Marginal effect	p-value	Coefficient latent variable	Marginal effect	p-value
Intercept		0.394	0.093	0.27	0.646	0.162	0.025	423.591	291.402	< 0.001
Age		0.016	0.004	0.003	0.011	0.003	0.009	-7.289	-5.014	< 0.001
EPIC Urinary Incontinence										
No side effects		ref	ref	ref	ref	ref	ref	ref	ref	ref
Slight side effects		-0.013	-0.003	0.875	0.078	0.019	0.296	39.329	27.056	0.086
Severe side effects		-0.199	-0.047	0.020	-0.183	-0.046	0.007	98.147	67.518	< 0.001
EPIC Urinary Irritative/ Obstructive										
No side effects		ref	ref	ref	ref	ref	ref	ref	ref	ref
Slight side effects		-0.073	-0.017	0.354	-0.08	-0.02	0.202	2.936	2.02	0.897
Severe side effects		-0.217	-0.051	0.070	-0.187	-0.047	0.067	58.286	40.097	0.127
EPIC Bowel										
No side effects		ref	ref	ref	ref	ref	ref	ref	ref	ref
Slight side effects		0.001	0.000	0.994	-0.108	-0.027	0.146	10.717	7.373	0.695
Severe side effects		0.081	0.019	0.550	0.003	0.001	0.978	-59.484	-40.921	0.132
EPIC Sexual										
No side effects		ref	ref	ref	ref	ref	ref	ref	ref	ref
Slight side effects		-0.109	-0.026	0.144	0.024	0.006	0.721	5.522	3.798	0.807
Severe side effects		0.025	0.006	0.811	0.026	0.007	0.767	38.434	26.44	0.169

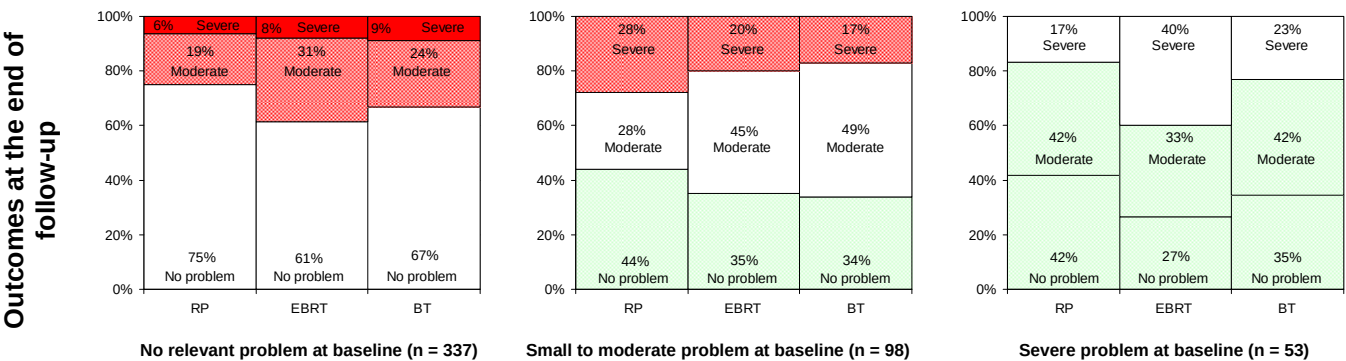
Abbreviations: SD= Standard deviation. WTP= Willingness to pay. EPIC= Expanded Prostate Cancer Index Composite.

*Kruskal Wallis to compare preferences scores and willingness to pay values among the side effects groups.

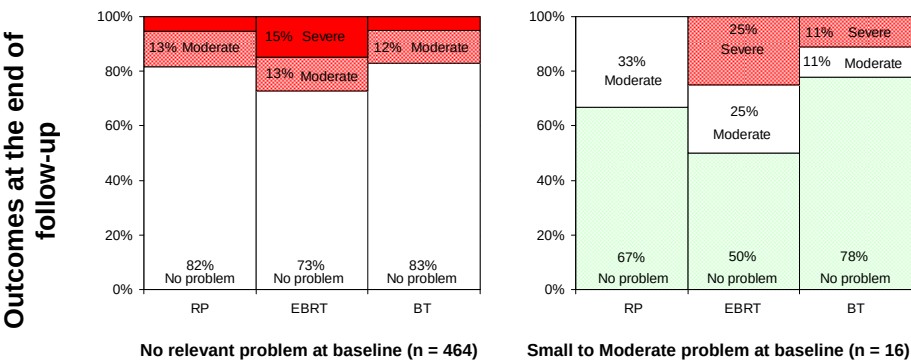
a) EPIC Urinary Incontinence



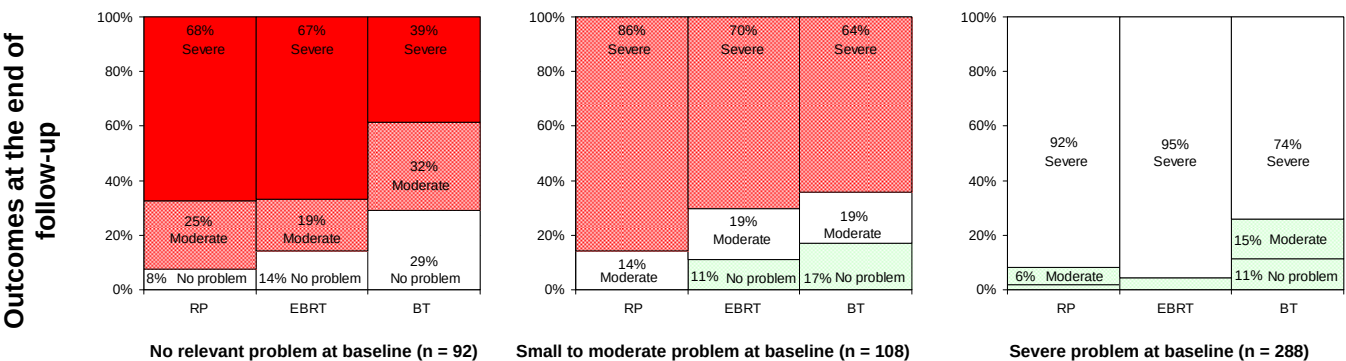
b) EPIC Urinary Irritative/Obstructive



c) EPIC Bowel



d) EPIC Sexual



Supplementary Material

[Click here to download Supplementary Material: AppendixA_SurveyInstrument_ProstateCancerPreferences_IJROBP.pdf](#)

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