International Journal of Radiation Oncology biology • physics

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Clinical Investigation

# Estimating Preferences for Treatments in Patients With Localized Prostate Cancer

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Received Jul 8, 2014, and in revised form Sep 25, 2014. Accepted for publication Sep 30, 2014.

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This study was supported 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.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

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Int J Radiation Oncol Biol Phys, Vol. 91, No. 2, pp. 277–287, 2015
0360-3016/$ - see front matter 
http://dx.doi.org/10.1016/j.ijrobp.2014.09.044

**Summary**

We estimated treatment preferences and willingness-to-pay attitudes of patients with localized prostate cancer who had been treated with radical prostatectomy, external radiation therapy, or brachytherapy, after 5 years of follow-up. To our knowledge, this is the first study to estimate preferences for brachytherapy and also one of the few studies to elicit willingness-to-pay attitudes toward prostate cancer treatments. Preferences elicited by any of the methods used showed statistically significant differences among treatments in favor of brachytherapy.

**Purpose:** Studies of patients' preferences for localized prostate cancer treatments have assessed radical prostatectomy and external radiation therapy, but none of them has evaluated brachytherapy. The aim of our study was to assess the preferences and willingness to pay of patients with localized prostate cancer who had been treated with radical prostatectomy, external radiation therapy, or brachytherapy, and their related urinary, sexual, and bowel side effects.

**Methods and Materials:** This was an observational, prospective cohort study with follow-up until 5 years after treatment. A total of 704 patients with low or intermediate risk localized prostate cancer were consecutively recruited from 2003 to 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 radiation therapy, and 263 with brachytherapy. Both time trade-off and standard gamble results indicated that the preferences of patients treated with brachytherapy were 0.06 utilities higher than those treated with radical prostatectomy ($P = .01$). Similarly, willingness-to-pay responses showed a difference of €57/month ($P = .004$) between these 2 treatments. Severe urinary incontinence presented an independent impact on the preferences elicited ($P < .05$), whereas no significant differences were found by bowel and sexual side effects.

**Conclusions:** Our findings indicate that urinary incontinence is the side effect with the highest impact on preferences and that brachytherapy and external radiation therapy are more valued than radical prostatectomy. These time trade-off and standard gamble preference 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. 

## Introduction

Prostate cancer is the most common cancer in men in the United States and European Union, with more than 350,000 and 200,000 cases, respectively, diagnosed annually (1). Earlier detection related to prostate-specific antigen (PSA) screening is reflected in the diagnosis of prostate cancer in younger patients at local stages (2). Patients with localized prostate cancer have the choice of very distinct treatments, such as surgery, radiation therapy, 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 HRQoL. 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). Prostate cancer patients' preferences or utilities can be directly elicited by using methods such as standard gamble (SG) and time trade-off (TTO) or indirectly by using multiattribute utility instruments (eg EQ-5D and Health Utility Index).

Although obtaining utilities by the indirect method with generic questionnaires is easier (4), their limitations in estimating prostate cancer patients' preferences have been repeatedly criticized (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).

Assessing utilities after prostate cancer treatment by measuring patients' health states with disease-specific HRQoL instruments has been published through 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 has 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 terms of 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 study of 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 WTP of patients with localized prostate cancer for radical prostatectomy, external radiation therapy, and brachytherapy, and the treatments' related urinary, sexual, and bowel side effects.

## Methods and Materials

### 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 with newly diagnosed localized prostate cancer (stages T1 or T2) treated with prostatectomy, external radiation therapy, or brachytherapy and with no previous transurethral prostate resection were included. Decisions about 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 trained to administer HRQoL and preference questionnaires. Full details of the interview are shown in Appendix EA (available online at www.redjournal.com). 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 pretreatment were recorded at clinical sites in the recruitment evaluation and included age, marital status, social class, PSA, Gleason score, and comorbidities, among other factors. Patients were staged (33) through directed history and physical examination. The definition of D'Amico et al (34) was used to divide patients into low and intermediate risk groups. A summary indicator of comorbidities was derived from a checklist of 12 common chronic conditions to classify patients into 1 of 3 categories (0-1, 2-3, $\geq$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 system (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" for 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 as having "no relevant problem," "small to moderate problem," (at least 1 distressful symptom), or having a "severe problem" (at least 1 very distressful symptom). Pretreatment and 5-year post-treatment evaluations were considered to define patients as having severe side effects (change from no relevant to severe problems), slight side effects (only 1 level worsening), or no side effects (patients without worsening).

### Time trade-off

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 1. 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, that is, $[1 - (2/10)]$. 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

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 of 100 people who chose the new cure, P people were completely cured (with all bothers related to the prostate disease disappearing completely) and the other [100 − P] people died because of this new cure. Would you risk trying this new cure?" The risk of death was varied in intervals of 10% (40%-10%) and then of 1% (5%-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 1 [1 − (100 − P)/100].

### Willingness-to-pay

The subject was asked to imagine he could obtain a cure and that he would not have to suffer the bothers of his prostate cancer; the cure was fully effective and there was no risk if he chose it but it was not publicly reimbursed, so he would have to pay for it. The WTP question was: "Let's imagine that your monthly net income is €1000. From this €1000 monthly net income, what amount, at the most, would you be willing to pay per month to not 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 radiation therapy, or brachytherapy) given measured covariates (prostate cancer characteristics, general health status, and sociodemographic variables). The final multinomial logistic regression model for calculating the propensity scores had c-statistic of 0.92 (95% confidence interval [CI] = 0.90-0.94) for radical prostatectomy, 0.81 (95% CI = 0.78-0.85) for external radiation therapy, and 0.85 (95% CI = 0.82-0.88) for brachytherapy, indicating good discriminant ability. Differences among treatment groups were tested using the $\chi^2$ 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 of 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 WTP among groups defined by sociodemographic variables, tumor characteristics, treatment, and side effects were performed using the 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 (*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 cooccurrence in some patients. These models were also adjusted by variables that 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 lay 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 allowed 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 was the best health and 0 was death (40). Statistical analysis was performed using SPSS version 12.0 software (SPSS, Chicago, IL) for Windows (Microsoft) and R Statistical software (www.r-project.org).

## 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 radiation therapy, and 263 with brachytherapy. There were statistically significant differences among treatment groups at baseline in several variables (age, social class, tumor characteristics, neoadjuvant hormone treatment, EPIC urinary incontinence, and sexual domains), which disappeared after adjustment by propensity score.

Figure 1 shows the proportions of patients who improved, remained stable, or worsened since baseline (pretreatment) 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 (Fig. 1, white bars), 30% worsened slightly (Fig. 1, light red bars), and 38% worsened severely (Fig. 1, dark red bars); whereas >65% of patients remained stable in the external and interstitial radiation therapy groups. More than half of the 50 patients with small to moderate incontinence at baseline did not present deterioration. A graph showing patients with severe urinary incontinence at baseline was not constructed due to small group size

**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 radiation therapy | Brachytherapy | *P* value* | Radical prostatectomy | External beam radiation therapy | Brachytherapy | *P* value† |
| Participants | 165 | 152 | 263 | | | | | |
| Patients characteristics | | | | | | | | |
| Mean ± SD age (y) | 64.2 (5.5) | 69.9 (5.3) | 66.8 (6.4) | < .001 | 67.7 (5.2) | 66.9 (5.3) | 66.4 (5.3) | .194 |
| <65 | 87 (53%) | 25 (16.4%) | 88 (33.5%) | < .001 | 28.5% | 27.4% | 28.9% | .489 |
| 65-70 | 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% | 31.0% | |
| Missing | 1 (0.6%) | 0 (0%) | 0 (0%) | | | | | |
| Marital status | | | | | | | | |
| No partner | 13 (11%) | 13 (9.5%) | 24 (10.2%) | .922 | 5.6% | 13.0% | 11.2% | .230 |
| Married or with partner | 105 (89%) | 124 (90.5%) | 211 (89.8%) | | 94.4% | 87.0% | 88.8% | |
| Social class | | | | | | | | |
| I-II Managerial-freelance professionals | 11 (9.4%) | 28 (20.6%) | 60 (25.5%) | .009 | 12.5% | 22.3% | 19.5% | .201 |
| III Skilled nonmanual occupations | 33 (28.2%) | 29 (21.3%) | 57 (24.3%) | | 32.1% | 22.2% | 23.0% | |
| IV-V Manual workers | 73 (62.4%) | 79 (58.1%) | 118 (50.2%) | | 55.4% | 55.6% | 57.5% | |
| No. with comorbidities (%) | | | | | | | | |
| 0-1 | 37 (31.4%) | 55 (40.2%) | 87 (37.0%) | .122 | 30.5% | 42.5% | 36.6% | .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% | |
| Mean PSA (ng/mL) (SD) | 7.7 (3) | 8.1 (3.2) | 6.8 (2.1) | < .001 | 7.6 (2.6) | 6.7 (2.7) | 6.2 (2.7) | .484 |
| Mean Gleason score (SD) | 6.3 (0.7) | 5.8 (1.1) | 5.5 (0.9) | < .001 | 5.8 (0.8) | 4.9 (0.8) | 4.4 (0.8) | .526 |
| No. with the following clinical T stages (%) | | | | | | | | |
| T1 | 107 (64.8%) | 88 (57.9%) | 214 (81.4%) | <.001 | 72.1% | 74.0% | 75.1% | .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% | |
| No. in the following risk groups (%) | | | | | | | | |
| Low | 74 (44.8%) | 86 (56.6%) | 236 (89.7%) | <.001 | 85.8% | 86.6% | 86.0% | .985 |
| Intermediate | 91 (55.2%) | 66 (43.4%) | 27 (10.3%) | | 14.2% | 13.4% | 14.0% | |
| No. receiving neoadjuvant hormone treatment (%) | | | | | | | | |
| 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%) | <.001 | 20.9% | 16.5% | 16.0% | |
| No. experiencing biochemical failure (%) | | | | | | | | |
| Yes | 38 (23%) | 53 (34.9%) | 63 (24%) | .026 | 14.7% | 34.9% | 29.7% | .004 |
| No | 127 (77%) | 99 (65.1%) | 199 (76%) | | 85.3% | 65.1% | 70.3% | |
| Mean quality of life score (SD) | | | | | | | | |
| EPIC urinary | | | | | | | | |
| Incontinence | 93.3 (16.3) | 96.1 (10.4) | 96.9 (10) | .028 | 92.7 (12) | 96.7 (12.2) | 97.0 (12.1) | .075 |
| Irritative/ obstructive | 93.4 (10.9) | 94.8 (11.3) | 94.2 (10.9) | .605 | 92.3 (11.1) | 95.9 (11.2) | 94.4 (11.2) | .140 |
| EPIC bowel | 98.0 (3.4) | 97.2 (6.6) | 97.0 (6.5) | .382 | 98.2 (5.9) | 97.9 (6.0) | 96.5 (6.0) | .088 |
| EPIC sexual | 58.8 (23.8) | 49.6 (23.9) | 49.5 (25.2) | .002 | 53.9 (24.6) | 51.6 (24.9) | 51.6 (24.9) | .825 |
| EPIC hormonal | 93.9 (9.2) | 94.2 (9.5) | 92.8 (10) | .348 | 92.7 (9.7) | 94.2 (9.9) | 93.6 (9.9) | .651 |

*Abbreviation:* EPIC = expanded prostate cancer index composite.

* $\chi^2$ test or one-way ANOVA among the 3 treatment groups.

† Differences in adjusted means and percentages among treatment groups were tested by linear or logistic regression models (with propensity score), respectively.

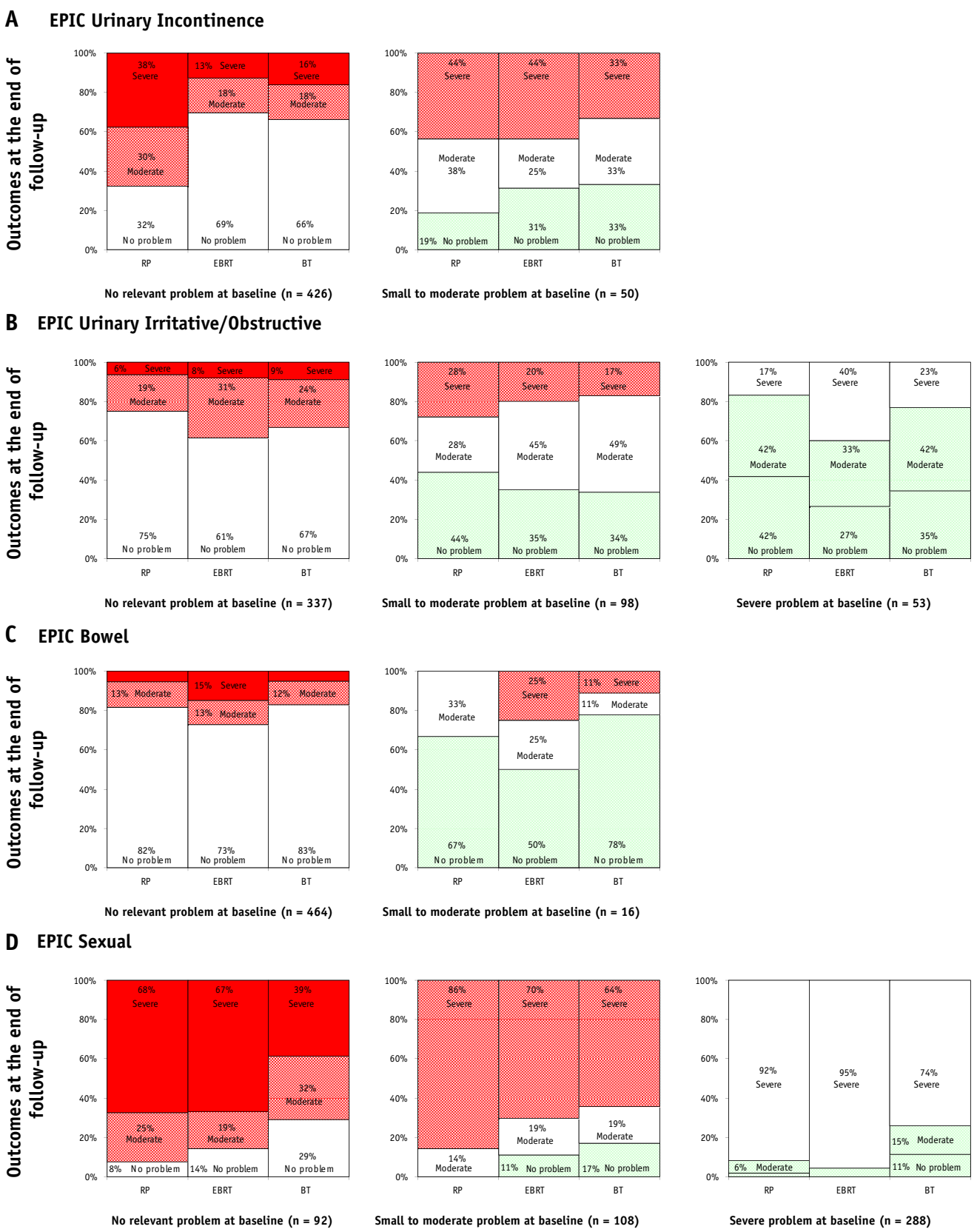


**Fig. 1.** Distribution of patients' symptom severity at the end of follow-up according to baseline symptom severity (pre-treatment evaluation). Percentage values in the bars represent the proportion of patients who reported problems at the end of follow-up. White bars show stable patients; green bars show those who improved from baseline; and light and dark red bars show those with slight and severe side effects, respectively. A color version of this figure is available at www.redjournal.org.

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

| Patient characteristics | Time trade-off | | Standard gamble | | WTP (€/month) | |
|---|---|---|---|---|---|---|
| | Mean (SD) | *P* value* | Mean (SD) | *P* value* | Mean (SD) | *P* value* |
| Sociodemographic characteristics | | | | | | |
| Age (y) | | | | | | |
| <65 | 0.96 (0.14) | .007 | 0.98 (0.09) | .083 | 52.25 (86.81) | <.001 |
| 65-70 | 0.97 (0.09) | | 0.98 (0.06) | | 30.33 (58.00) | |
| ≥70 | 0.98 (0.07) | | 0.98 (0.09) | | 24.82 (67.37) | |
| Marital status | | | | | | |
| No partner | 0.99 (0.05) | .117 | 0.99 (0.08) | .033 | 31.60 (64.44) | .681 |
| Married or with partner | 0.97 (0.11) | | 0.98 (0.08) | | 36.42 (73.97) | |
| Social class | | | | | | |
| I-II Managerial-freelance professionals | 0.97 (0.10) | .464 | 0.97 (0.10) | .595 | 47.39 (84.79) | .147 |
| III Skilled nonmanual 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) | .211 | 0.98 (0.08) | .863 | 37.37 (75.50) | .933 |
| Intermediate risk | 0.96 (0.12) | | 0.98 (0.09) | | 32.93 (67.28) | |
| No. with comorbidities | | | | | | |
| 0-1 | 0.97 (0.10) | .414 | 0.99 (0.05) | .382 | 38.80 (89.56) | .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 test was used to compare preference scores and willingness-to-pay values among sociodemographic and clinical variables.

(n = 12). Regarding urinary irritative obstructive side effects, most occurrences of deterioration 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 to 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, whereas 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 radiation therapy and brachytherapy compared to radical prostatectomy. In this model, patients treated with radiation therapy (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, whereas significance was marginal for irritative/obstructive symptoms. No differences were found according to 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 favor 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 versus 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, whereas patients treated with brachytherapy were willing to sacrifice 3% ($P<.001$). Differences between them were higher after adjusting for propensity score (0.06 instead of 0.02 utilities). Also, the prostatectomy patients were willing to pay the highest value (€47.67/month) to not suffer bothers, whereas brachytherapy patients were willing to pay almost €16/month less ($P<.001$). After adjusting by propensity score, a difference of €57/month ($P = .004$) was estimated between these 2 treatments. Regarding external radiation therapy, statistically significant higher utilities than for radical prostatectomy were shown by TTO, and *P* value was only barely above .05 for WTP. Previous studies comparing these treatments by using indirect methods reported contradictory results (6, 19, 22). The small differences between external radiation therapy

**Table 3** Preferences and willingness-to-pay values according to treatment received

| | Time trade-off | | | Standard gamble | | | WTP (€/month) | | |
|---|---|---|---|---|---|---|---|---|---|
| Bivariate analysis | Mean | (SD) | *P* value* | Mean | (SD) | *P* value* | Mean | (SD) | *P* value* |
| Radical prostatectomy | 0.95 | (0.13) | <.001 | 0.98 | (0.07) | .01 | 47.67 | (82.01) | <.001 |
| External radiation therapy | 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 | <.001 | 1.318 | 0.357 | <.001 | −31.749 | −21.841 | .141 |
| Radical prostatectomy | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| External radiation therapy | 0.234 | 0.058 | .027 | 0.106 | 0.029 | .212 | −58.296 | −40.103 | .059 |
| Brachytherapy | 0.249 | 0.061 | .012 | 0.215 | 0.058 | .010 | −82.542 | −56.783 | .004 |

*Abbreviations:* Ref = reference; SD = standard deviation; WTP = willingness to pay.
* Kruskal Wallis test was used to compare preferences scores and willingness-to-pay values among the 3 treatment groups.
† Adjusted by propensity scores.

and brachytherapy coefficients indicated that both were preferred to prostatectomy.

The patients without urinary side effects were willing to give up 2% to 3% of their remaining life, whereas 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 2 extreme groups were similar: 0.047 ($P=.02$) for incontinence and 0.051 ($P=.07$) for irritative/obstructive symptoms. Similarly, SG results showed that patients without urinary side effects were indifferent toward continuing with their present health status or taking a 1% to 2% chance of death, on average, whereas 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 with 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 $P<.001$).

We did not find any statistically significant differences between utilities in patients with and those without bowel and sexual side effects. In contrast to 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 and were therefore without a definition of side effects based on a before-and-after comparison. This is especially relevant to distinguish the sexual dysfunction associated with 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, because 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 (eg surgery is prescribed for younger patients and brachytherapy for patients at lower risk). Propensity score methods are being widely recommended in observational studies (41-43) to account for treatment selection bias and, thus, to 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 of 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 infra-estimation 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 applied equally to the patients regardless of the treatment undertaken. Furthermore, the consistency between results from TTO and SG provides support for the validity of utilities obtained. 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

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

| Bivariate analysis | % | Time trade-off Mean | (SD) | *P* value* | Standard gamble Mean | (SD) | *P* value* | WTP (€/month) Mean | (SD) | *P* value* |
|---|---|---|---|---|---|---|---|---|---|---|
| EPIC urinary incontinence | | | | | | | | | | |
| No side effects (n=295) | 60.5% | 0.98 | (0.10) | <.001 | 0.98 | (0.09) | <.001 | 27.69 | (68.51) | <.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) | <.001 | 0.99 | (0.07) | <.001 | 32.70 | (69.19) | .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) | .545 | 0.98 | (0.07) | .322 | 35.90 | (73.68) | .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) | .179 | 0.98 | (0.09) | .876 | 32.56 | (70.64) | .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 | .27 | 0.646 | 0.162 | .025 | 423.591 | 291.402 | <.001 |
| Age | 0.016 | 0.004 | .003 | 0.011 | 0.003 | .009 | −7.289 | −5.014 | <.001 |
| EPIC urinary incontinence | | | | | | | | | |
| No side effects | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Slight side effects | −0.013 | −0.003 | .875 | 0.078 | 0.019 | .296 | 39.329 | 27.056 | .086 |
| Severe side effects | −0.199 | −0.047 | .020 | −0.183 | −0.046 | .007 | 98.147 | 67.518 | <.001 |
| EPIC Urinary irritative/obstructive | | | | | | | | | |
| No side effects | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Slight side effects | −0.073 | −0.017 | .354 | −0.08 | −0.02 | .202 | 2.936 | 2.02 | .897 |
| Severe side effects | −0.217 | −0.051 | .070 | −0.187 | −0.047 | .067 | 58.286 | 40.097 | .127 |
| EPIC Bowel | | | | | | | | | |
| No side effects | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Slight side effects | 0.001 | 0.000 | .994 | −0.108 | −0.027 | .146 | 10.717 | 7.373 | .695 |
| Severe side effects | 0.081 | 0.019 | .550 | 0.003 | 0.001 | .978 | −59.484 | −40.921 | .132 |
| EPIC sexual | | | | | | | | | |
| No side effects | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Slight side effects | −0.109 | −0.026 | .144 | 0.024 | 0.006 | .721 | 5.522 | 3.798 | .807 |
| Severe side effects | 0.025 | 0.006 | .811 | 0.026 | 0.007 | .767 | 38.434 | 26.44 | .169 |

*Abbreviations:* EPIC = expanded prostate cancer index composite; Ref = reference; SD = standard deviation; WTP = willingness to pay.
* Kruskal-Wallis test was used to compare preferences scores and willingness-to-pay values among the side effects groups.

follow-up. This cohort (32) showed a stable side effect pattern from the second to fifth year, except for a late worsening in incontinence for brachytherapy patients and in sexual function for external radiation therapy patients, 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 involved 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 of the concept of probability (12). However, the interviewer was 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 that was minimized by the high response rate obtained (90%). Finally, our results may have limited generalizability for other countries, as the impact of symptoms in the preferences may be affected by cultural dissimilarities.

## Conclusions

This study provides preferences and WTP responses from patients treated for localized prostate cancer with radical prostatectomy, external radiation therapy, 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 to elicit WTP values from patients with

localized prostate cancer. In conclusion, our findings indicated that urinary incontinence is the side effect with highest impact on preferences, and brachytherapy and external radiation therapy are more highly valued than radical prostatectomy. These TTO and SG preference assessments, as well as the estimation of WTP, reflect the patients' preferences according to side effects of different treatments for localized prostate cancer, and they are useful for performing cost-utility or cost−benefit analyses (47), which can guide health policy decisions.

## References


1. International Agency for Research on Cancer. GLOBOCAN website. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed June 17, 2014.
2. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst* 2009;101:1280-1283.
3. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250-1261.
4. Krahn M, Ritvo P, Irvine J, et al. Patient and community preferences for outcomes in prostate cancer: Implications for clinical policy. *Med Care* 2003;41:153-164.
5. Shimizu F, Fujino K, Ito YM, et al. Factors associated with variation in utility scores among patients with prostate cancer. *Value Health* 2008;11:1190-1193.
6. Jayadevappa R, Schwartz JS, Chhatre S, et al. Association between utility and treatment among patients with prostate cancer. *Qual Life Res* 2010;19:711-720.
7. Krahn M, Bremner KE, Tomlinson G, et al. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. *Qual Life Res* 2007;16:509-522.
8. Albertsen PC, Nease RF Jr, Potosky AL. Assessment of patient preferences among men with prostate cancer. *J Urol* 1998;159:158-163.
9. Bremner KE, Chong CA, Tomlinson G, et al. A review and meta-analysis of prostate cancer utilities. *Med Decis Making* 2007;27:288-298.
10. Bhatnagar V, Stewart ST, Bonney WW, et al. Treatment options for localized prostate cancer: quality-adjusted life years and the effects of lead-time. *Urology* 2004;63:103-109.
11. Bruner DW, Hanlon A, Mazzoni S, et al. Predictors of preferences and utilities in men treated with 3D-CRT for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:34-42.
12. Elstein AS, Chapman GB, Chmiel JS, et al. Agreement between prostate cancer patients and their clinicians about utilities and attribute importance. *Health Expect* 2004;7:115-125.
13. Saigal C, Gornbein J, Litwin MS. Patient utilities for complications do not predict treatment choice in men with clinically localized prostate cancer. *J Clin Outcomes Manag* 2001;8:17-22.
14. Saigal CS, Gornbein J, Nease R, et al. Predictors of utilities for health states in early stage prostate cancer. *J Urol* 2001;166:942-946.
15. Sommers BD, Beard CJ, D'Amico AV, et al. Decision analysis using individual patient preferences to determine optimal treatment for localized prostate cancer. *Cancer* 2007;110:2210-2217.
16. Sommers BD, Beard CJ, D'Amico AV, et al. Predictors of patient preferences and treatment choices for localized prostate cancer. *Cancer* 2008;113:2058-2067.
17. Dale W, Basu A, Elstein A, et al. Predicting utility ratings for joint health States from single health States in prostate cancer: Empirical testing of 3 alternative theories. *Med Decis Making* 2008;28:102-112.
18. Saigal CS, Gornbein J, Reid K, et al. Stability of time trade-off utilities for health states associated with the treatment of prostate cancer. *Qual Life Res* 2002;11:405-414.
19. Krahn MD, Bremner KE, Tomlinson G, et al. Utility and health-related quality of life in prostate cancer patients 12 months after radical prostatectomy or radiation therapy. *Prostate Cancer Prostatic Dis* 2009;12:361-368.
20. Ku J, Krahn M, Trachtenberg J, et al. Changes in health utilities and health-related quality of life over 12 months following radical prostatectomy. *Can Urol Assoc J* 2009;3:445-452.
21. Basu A, Dale W, Elstein A, et al. A time tradeoff method for eliciting partner's quality of life due to patient's health states in prostate cancer. *Med Decis Making* 2010;30:355-365.
22. Krahn MD, Bremner KE, Alibhai SM, et al. A reference set of health utilities for long-term survivors of prostate cancer: Population-based data from Ontario, Canada. *Qual Life Res* 2013;22:2951-2962.
23. Report of the NOAA panel on contingent valuation. *Fed Regist* 1993;58:4601-4614.
24. Diener A, O'Brien B, Gafni A. Health care contingent valuation studies: a review and classification of the literature. *Health Econ* 1998;7:313-326.
25. Drummond M, O'Brien B, Stoddart GL, et al. Methods for the Economic Evaluation of Health Care Programmes. 2nd ed. Oxford: Oxford University Press; 1997.
26. Yasunaga H, Ide H, Imamura T, et al. Benefit evaluation of mass screening for prostate cancer: Willingness-to-pay measurement using contingent valuation. *Urology* 2006;68:1046-1050.
27. Yasunaga H. Willingness to pay for mass screening for prostate cancer: A contingent valuation survey. *Int J Urol* 2008;15:102-105.
28. Neumann PJ, Cohen JT, Hammitt JK, et al. Willingness-to-pay for predictive tests with no immediate treatment implications: A survey of US residents. *Health Econ* 2010;21:238-251.
29. Li C, Zeliadt SB, Hall IJ, et al. Willingness to pay for prostate cancer treatment among patients and their family members at 1 year after diagnosis. *Value Health* 2012;15:716-723.
30. Ferrer M, Suarez JF, Guedea F, et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:421-432.
31. Pardo Y, Guedea F, Aguilo F, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. *J Clin Oncol* 2010;28:4687-4696.
32. Ferrer M, Guedea F, Suarez JF, et al. Quality of life impact of treatments for localized prostate cancer: Cohort study with a 5 year follow-up. *Radiother Oncol* 2013;108:306-313.
33. Green FL, Page DL, Fleming ID, et al. Prostate. AJCC Cancer Staging Manual. 6th ed. New York: Springer-Verlag; 2002.
34. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-974.
35. Domingo-Salvany A, Regidor E, Alonso J, et al. Proposal for a social class measure. Working Group of the Spanish Society of Epidemiology and the Spanish Society of Family and Community Medicine. *Aten Primaria* 2000;25:350-363.
36. Ferrer M, Garin O, Pera J, et al. Evaluación de la calidad de vida de los pacientes con cáncer de próstata localizado: Validación de la versión española del cuestionario EPIC [Evaluation of the quality of life of patients with localizad prostate cancer: Validation of the Spanish version of the EPIC]. *Med Clin (Barc)* 2009;132:128-135.
37. Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;56:899-905.
38. Instituto Nacional de Estadistica website. Survey on disability, personal autonomy and dependency situations, 2008. Available at: http://www.ine.es/jaxi/menu.do?L=0&type=pcaxis&path=/t15/p418&file=inebase. Accessed February 24, 2009.

39. Instituto Nacional de Estadística website. Annual survey of salary structure. Available at: http://www.ine.es/prensa/np601.pdf. Accessed February 24, 2009.
40. Greene WH. Marginal effects in the censored regression model. *Econ Lett* 1999;64:43-49.
41. Chamie K, Kurzrock EA, Evans CP, et al. Secondary malignancies among nonseminomatous germ cell tumor cancer survivors. *Cancer* 2011;117:4219-4230.
42. Reeves MJ, Gargano JW, Luo Z, et al. Effect of pretreatment with statins on ischemic stroke outcomes. *Stroke* 2008;39:1779-1785.
43. Yeh RW, Kennedy K, Spertus JA, et al. Do postmarketing surveillance studies represent real-world populations? A comparison of patient characteristics and outcomes after carotid artery stenting. *Circulation* 2011;123:1384-1390.
44. Crook JM, Gomez-Iturriaga A, Wallace K, et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy versus Interstitial Radiation Intervention Trial. *J Clin Oncol* 2011;29:362-368.
45. Wilt TJ. Can randomized treatment trials in early stage prostate cancer be completed? *Clin Oncol (R Coll Radiol)* 1998;10:141-143.
46. Denberg TD, Melhado TV, Steiner JF. Patient treatment preferences in localized prostate carcinoma: The influence of emotion, misconception, and anecdote. *Cancer* 2006;107:620-630.
47. Garcia-Altes A, Jovell AJ. Could we measure the efficiency of prostate cancer treatment? A critical appraisal of economic evaluation studies. *Prostate Cancer Prostatic Dis* 2001;4:217-220.