

CLINICAL INVESTIGATION

Prostate

## 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

MONTSERRAT FERRER, M.D., PH.D.,<sup>\*†</sup> JOSÉ FRANCISCO SUÁREZ, M.D.,<sup>‡</sup> FERRAN GUEDEA, M.D., PH.D.,<sup>§</sup>  
PABLO FERNÁNDEZ, M.D.,<sup>||</sup> VÍCTOR MACÍAS, M.D.,<sup>¶</sup> ALFONSO MARIÑO, M.D.,<sup>#</sup>  
ASUNCIÓN HERVAS, PH.D.,<sup>\*\*</sup> ISMAEL HERRUZO, M.D., PH.D.,<sup>††</sup> MARÍA JOSÉ ORTIZ, M.D., PH.D.,<sup>‡‡</sup>  
HUMBERTO VILLAVICENCIO, PH.D.,<sup>§§</sup> JORDI CRAVEN-BRATLE, M.D., PH.D.,<sup>|||</sup>  
OLATZ GARIN, M.P.H.,<sup>\*†</sup> FERRAN AGUILÓ, M.D., PH.D.,<sup>‡</sup> AND THE MULTICENTRIC SPANISH GROUP OF  
CLINICALLY LOCALIZED PROSTATE CANCER

\*Unidad de Investigación en Servicios Sanitarios, IMIM-Hospital del Mar, Barcelona, Spain; <sup>†</sup>CIBER en Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; <sup>‡</sup>Servicio de Urología, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; <sup>§</sup>Servicio de Oncología Radioterápica, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain; <sup>||</sup>Servicio de Oncología Radioterápica, Instituto Oncológico de Guipúzcoa, San Sebastián, Spain; <sup>¶</sup>Servicio de Oncología Radioterápica, Capio Hospital General de Catalunya, Sant Cugat del Valles, Spain; <sup>#</sup>Servicio de Oncología Radioterápica, Centro Oncológico de Galicia, A Coruña, Spain; <sup>\*\*</sup>Servicio de Oncología Radioterápica, Hospital Ramon y Cajal, Madrid, Spain; <sup>††</sup>Servicio de Oncología Radioterápica, Hospital Regional Carlos Haya, Málaga, Spain; <sup>‡‡</sup>Servicio de Oncología Radioterápica, Hospital Virgen del Rocío, Sevilla, Spain; <sup>§§</sup>Servicio de Urología, Fundación Puigvert, Barcelona, Spain; and <sup>|||</sup>Servicio de Oncología Radioterápica, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

**Purpose:** To compare treatment impact on health-related quality of life (HRQL) in patients with localized prostate cancer, from before treatment to 2 years after the intervention.

**Methods and Materials:** This was a longitudinal, prospective study of 614 patients with localized prostate cancer treated with radical prostatectomy (134), three-dimensional external conformal radiotherapy (205), and brachytherapy (275). The HRQL questionnaires administered before and after treatment (months 1, 3, 6, 12, and 24) were the Medical Outcomes Study 36-Item Short Form, the Functional Assessment of Cancer Therapy (General and Prostate Specific), the Expanded Prostate Cancer Index Composite (EPIC), and the American Urological Association Symptom Index. Differences between groups were tested by analysis of variance and within-group changes by univariate repeated-measures analysis of variance. Generalized estimating equations (GEE) models were constructed to assess between-group differences in HRQL at 2 years of follow-up after adjusting for clinical variables. **Results:** In each treatment group, HRQL initially deteriorated after treatment with subsequent partial recovery. However, some dimension scores were still significantly lower after 2 years of treatment. The GEE models showed

Reprint requests to: Montserrat Ferrer, M.D., Unitat de Recerca en Serveis Sanitaris, IMIM-Hospital del Mar, Parc de Recerca Biomèdica de Barcelona (despatx 144), Doctor Aiguader, 88, Barcelona 08003, Spain. Tel: (+34) 933-160-740; Fax: (+34) 933-160-797; E-mail: mferrer@imim.es

Funded by Departament d'Universitats, Recerca i Societat de la Informació de la Generalitat de Catalunya (DURSI-GENCAT) (2005-SGR-00491), Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM) 086/24/2000, Fondo de Investigación Sanitaria (FIS) PI020668. A. Pont is supported by a support contract through the National Health System, Instituto Nacional Carlos III CA06/0081.

Presented at the XXIV Annual Meeting of the Spanish Society of Epidemiology, July 4–7, 2006, Logroño, Spain; the 13th Annual Scientific Conference of the International Society for Quality of Life Research, October 10–14, 2006, Lisboa, Portugal; the 2007 Prostate Cancer Symposium, American Society of Clinical Oncology, February 22–24, 2007, Orlando, FL; and the 22nd Annual Meeting of the European Society of Urology, March 21–24 2007, Berlin, Germany.

Participants in the Multicentric Spanish Group of Clinically Localized Prostate Cancer: Jordi Alonso, Oriol Cunillera, Montse Ferrer, Olatz Garín, Angels Pont (IMIM-Hospital del Mar); Ana Boladeras, Ferran Ferrer, Ferran Guedea, Victoria Eugenia Padín, Joan Pera, Montse Ventura (Institut Català d'Oncologia); Ferran Aguiló, José Francisco Suárez (Hospital Universitari de Bellvitge); Sergio Pastor, Josep Maria Prats (Corporació de Salut Maresme i la Selva); Javier Ponce de León, Humberto Villavicencio (Fundación Puigvert); Jose Emilio Batista (Fundación Teknon); Jordi Craven-Bratle, Gemma Sancho (Hospital de la Santa Creu i Sant Pau); Belen de Paula, Pablo Fernández (Instituto Oncológico de Guipúzcoa); Benjamin Guix (Fundación IMOR); Ismael Herruzo (Hospital Regional Carlos Haya); Helena Hernandez, Victor Muñoz (Hospital Meixoeiro-Complejo CHUVI); Asunción Hervas, Alfredo Ramos (Hospital Ramon y Cajal); Víctor Macías, Pilar Marcos (Capio Hospital General de Catalunya); Alfonso Mariño (Centro Oncológico de Galicia); María José Ortiz (Hospital Virgen del Rocío); Pedro J. Prada (Hospital Universitario Central de Asturias).

Conflict of interest: none.

Received Oct 2, 2007, and in revised form Dec 21, 2007. Accepted for publication Dec 22, 2007.

that, compared with the brachytherapy group, radical prostatectomy patients had worse EPIC sexual summary and urinary incontinence scores ( $-20.4$  and  $-14.1$ ;  $p < 0.001$ ), and external radiotherapy patients had worse EPIC bowel, sexual, and hormonal summary scores ( $-3.55$ ,  $-5.24$ , and  $-1.94$ ;  $p < 0.05$ ). Prostatectomy patients had significantly better EPIC urinary irritation scores than brachytherapy patients ( $+4.16$ ;  $p < 0.001$ ).

**Conclusions:** Relevant differences between treatment groups persisted after 2 years of follow-up. Radical prostatectomy had a considerable negative effect on sexual functioning and urinary continence. Three-dimensional conformal radiotherapy had a moderate negative impact on bowel functioning, and brachytherapy caused moderate urinary irritation. These results provide relevant information for clinical decision making. © 2008 Elsevier Inc.

**Quality of life, Radical prostatectomy, External beam radiotherapy, Prostate brachytherapy, EPIC.**

## INTRODUCTION

Prostate cancer is the second most common cancer after lung cancer in men in the European Union. The European 5-year relative survival rate increased from 55% for the period 1983–1985 to 68% for 1992–1994 (1). The use of serum tests for prostate-specific antigen (PSA) means that disease is being diagnosed that would otherwise remain clinically undetectable (2–8). This has led to an increase in incidence and an increasing proportion of early, good-prognosis prostate cancers.

Although radical prostatectomy was traditionally considered the treatment of choice for prostate cancer in men with a life expectancy of 10 years or more (9–12), technical advances in the last decade have led to a renewed interest in brachytherapy and external beam radiotherapy, both of which are becoming more widely used. In this context, it is no longer clear which treatment is preferable for localized prostate cancer, particularly because the different treatments have shown good results in terms of cancer control (13–18). The similarity in survival rates associated with the different treatments and the fact that prostate cancer is increasingly asymptomatic at diagnosis have led to growing interest in evaluating the impact of treatment on patient quality of life.

Published studies comparing the impact of alternative treatments on the health-related quality of life (HRQL) of patients with localized prostate cancer have had some methodologic problems. Most did not include a pretreatment evaluation of HRQL (19–25), despite the fact that the comparison of scores before and after the intervention is fundamental to drawing conclusions regarding effectiveness. Furthermore, many longitudinal studies have only followed patients for up to 1 year (22, 26–28), whereas repeated measurement of HRQL over longer follow-up periods would provide evidence regarding modification in results over time. The objective of this study was to compare the impact of radical prostatectomy, brachytherapy, and three-dimensional (3D) external beam radiotherapy on the HRQL of patients with localized prostate cancer, from before treatment to 2 years after the intervention.

## METHODS AND MATERIALS

### Study design

This was a 2-year follow-up prospective study of organ-confined prostate cancer patients treated with radical retropubic prostatectomy, external beam radiotherapy, or interstitial brachytherapy.

### Patients

Between April 2003 and March 2005, a total of 841 consecutive outpatients with clinically localized prostate cancer were recruited in

10 Spanish hospitals (two urology and eight radiation Oncology departments). Inclusion criteria were Stages T1 or T2 and no previous transurethral prostate resection. The study was approved by the ethics review boards of the participating hospitals, and written informed consent was obtained from patients, according to the 2000 revision of the Helsinki Declaration. Patients were staged according to the American Joint Committee on Cancer 6th edition clinical staging guidelines (29) with a directed history and physical examination. All patients underwent serum PSA determination and Gleason score histologic grading. The definition of D'Amico *et al.* (13) was used to classify patients into risk groups: low-risk patients were T1c or T2a, PSA  $<10$  ng/mL and Gleason  $<6$ ; intermediate-risk patients were T2b, PSA 11–20 ng/mL or Gleason 7; and high-risk patients were T2c, PSA  $>20$  ng/mL or Gleason  $>7$ .

### Treatments

The decision regarding treatment selection was made jointly by the patients and the health professionals. All patients included in the surgery group underwent radical retropubic prostatectomy. Nerve-sparing techniques were used at the discretion of the operating surgeon. External beam radiation was carried out with the 3D conformal technique. Patients were treated in a supine position by immobilizing feet and legs. Data from a computed tomography (CT) scan performed with the patient in the treatment position were entered into a 3D treatment-planning system to outline prostate, bladder, and rectum on each slice. Seminal vesicles and regional lymphatics were also contoured if a high risk of involvement was suspected. Applied margins (mean = 10.1 mm, SD = 1.8 mm) were used to obtain prostate planning target volume (PTV). Custom blocking with Cerrobend blocks or multileaf collimators were designed using beam's eye view, and additional margins were adjusted to provide a minimum dose of 95% to the prostate PTV. Treatment was delivered in 1.8 to 2.0-Gy daily fractions, 5 days per week, to a mean (SD) dose of 74.03 (4.3) Gy to the prostate PTV. Off-line setup control was assessed weekly by comparing orthogonal portal images with the corresponding digitally reconstructed radiographs. In the brachytherapy group, all men received brachytherapy alone with  $^{125}\text{I}$ . The prescription dose was 144 Gy to the reference isodose (100%) according to the TG-T43 (30). The median dose of D90 and V100% was 152 Gy and 93%, respectively.

### HRQL assessment

Health-related quality of life questionnaires were administered centrally by telephone interview before treatment and during follow-up (1, 3, 6, 12, and 24 months after treatment). Questionnaires administered were the Medical Outcomes Study 36-Item Short Form (SF-36), the Functional Assessment of Cancer Therapy-General and -Prostate Specific (FACT-G and FACT-P, respectively), the Expanded Prostate Cancer Index Composite (EPIC), and the American Urological Association Symptom Index (AUA-7).

The SF-36 (version 2) contains 36 items covering eight dimensions of HRQL (31–33): physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality,

Table 1. Patient characteristics at pretreatment evaluation and response rates at each evaluation

Variable	Radical prostatectomy	3D Conformal radiotherapy	Brachytherapy	<i>p</i>
Participants ( <i>n</i> )	134	205	275	
Clinical characteristics				
Age (y)	64.0 (5.5)	69.2 (5.5)	66.9 (6.5)	<0.001*†‡
PSA (ng/mL)	7.9 (3.3)	10.1 (7.9)	6.9 (2.3)	<0.001*†‡
Gleason score	6.8 (6.2)	6.0 (1.1)	5.7 (4.4)	0.042 <sup>†</sup>
Clinical T stage				<0.001*†‡
T1	88 (65.7)	106 (51.7)	224 (81.5)	
T2	46 (34.3)	95 (46.3)	51 (18.5)	
Tx	0 (0)	4 (2.0)	0 (0)	
Risk group				<0.001*†‡
Low	58 (43.3)	98 (47.8)	241 (87.6)	
Intermediate	71 (53.0)	70 (34.1)	32 (11.6)	
High	5 (3.7)	37 (18.0)	2 (0.7)	
Neoadjuvant hormonal therapy	11 (8.2)	69 (33.7)	87 (31.6)	<0.001*†
Antiandrogen	3 (2.2)	6 (2.9)	9 (3.3)	
LHRH analogue	1 (0.7)	2 (1.0)	2 (0.7)	
Antiandrogen and LHRH analogue	7 (5.2)	61 (29.8)	76 (27.6)	
HRQL scores				
SF-36 PCS	53.3 (6.0)	52.3 (6.2)	53.8 (5.5)	0.022 <sup>‡</sup>
SF-36 MCS	53.9 (6.0)	54.6 (5.7)	53.9 (6.2)	0.407
FACT-G	80.3 (7.5)	79.6 (9.9)	79.6 (8.4)	0.723
FACT-P	39.3 (4.0)	38.7 (4.6)	39.3 (4.0)	0.246
EPIC urinary	93.8 (10.8)	95.9 (7.0)	95.2 (8.8)	0.096
Urinary irritative	94.4 (9.7)	96.2 (7.1)	95.0 (9.4)	0.167
Urinary incontinence	95.1 (13.7)	95.7 (10.6)	96.9 (9.9)	0.229
EPIC bowel	98.0 (3.6)	97.2 (6.1)	97.0 (6.2)	0.201
EPIC sexual	58.2 (24.0)	49.1 (24.4)	48.5 (25.2)	< 0.001*†
EPIC hormonal	93.8 (9.2)	93.2 (10.3)	92.9 (9.9)	0.673
AUA-7	6.9 (6.1)	6.4 (5.9)	5.8 (5.4)	0.201
HRQL interviews response rate				
Pretreatment	134 (100)	205 (100)	275 (100)	
Follow-up month 1	70 (52.2)	88 (42.9)	146 (53.1)	0.068
Follow-up month 3	124 (92.5)	186 (90.7)	256 (93.1)	0.626
Follow-up month 6	118 (88.1)	180 (87.8)	247 (89.8)	0.755
Follow-up month 12	121 (90.3)	184 (89.8)	255 (92.7)	0.480
Follow-up month 24	122 (91.0)	179 (87.3)	240 (87.3)	0.494

**Abbreviations:** 3D = three-dimensional; LHRH = luteinizing hormone-releasing hormone; HRQL = health-related quality of life; SF-36 = Medical Outcomes Study 36-Item Short Form; PCS = physical component summary; MCS = mental component summary; FACT-G, FACT-P = Functional Assessment of Cancer Therapy (General and Prostate Specific); EPIC = Expanded Prostate Cancer Index Composite; AUA-7 = American Urological Association Symptom Index.

Values are mean (SD) or *n* (%) unless otherwise noted. One-way analysis of variance to compare continuous variables among the three treatment groups; Tukey studentized range (honestly significant) *post hoc* comparisons with *p* < 0.05 for \*radical prostatectomy vs. three-dimensional (3D) conformal radiotherapy; †radical prostatectomy vs. brachytherapy; and ‡brachytherapy vs. 3D conformal radiotherapy.

social functioning, role limitations due to emotional problems, and mental health. For each dimension a score ranging from 0 (worst measured health) to 100 (best measured health) was calculated. Physical and mental component summaries (PCS and MCS) were constructed from the eight SF-36 dimensions, using recommended scoring algorithms (33). Summary scores were standardized to have a mean of 50 and SD of 10 in the U.S. general population.

The FACT-G version 4.0 (34) was designed to measure the HRQL of cancer patients. It consists of 27 items in four dimensions measuring physical, social/familial, emotional, and functional well-being. The prostate module (FACT-P) is specific for patients with prostate cancer (35, 36) and contains 12 questions about urinary symptoms and bowel and sexual function. Scores range from 0 to 108 on the FACT-G and from 0 to 48 on the FACT-P, with 0 representing perfect health.

The EPIC instrument (50 items) (37) was constructed by expanding the University of California-Los Angeles Prostate Cancer Index (38) to assess function and bother in the four domains (urinary,

bowel, sexual, and hormonal). For each domain a summary score and two subscale scores (function and bother) were constructed. In addition, two urinary scales that distinguish irritative/obstructive symptoms and incontinence were obtained, as recommended by the developers of the questionnaire. All EPIC items are answered on a 5-point Likert scale. Scores were transformed linearly to a scale of 0 to 100, with higher scores indicating better HRQL.

The AUA-7 was developed to assess urinary obstruction (39, 40). It contains seven items, and the score ranges from 0 to 35, with higher scores denoting a worse health state.

#### Sample size calculation

Sample size calculations were based on expected between-group differences on the EPIC questionnaire because it was designed to evaluate the impact of treatment on the quality of life of patients with clinically localized prostate cancer (37). It was calculated that

Table 2. Repeated-measures analysis of variance of quality-of-life measures for men treated with radical prostatectomy

Quality of life measure	Mean (SE)					<i>p</i> (ANOVA)	<i>p</i> (vs. pretreatment)*			
	Pretreatment	Month 3	Month 6	Month 12	Month 24		Month 3	Month 6	Month 12	Month 24
SF-36 PCS	54.0 (0.5)	51.9 (0.5)	53.0 (0.5)	52.5 (0.5)	50.6 (0.8)	0.004	0.001	0.986	0.164	<0.001
SF-36 MCS	53.3 (0.6)	53.0 (0.8)	53.3 (0.9)	55.3 (0.7)	54.9 (0.8)	0.005	1.0	1.0	0.143	0.331
FACT-G	79.7 (0.8)	78.0 (1.0)	78.9 (1.0)	79.8 (1.1)	76.6 (1.1)	0.051	—	—	—	—
FACT-P	39.8 (0.4)	35.6 (0.5)	37.2 (0.4)	37.9 (0.4)	37.2 (0.5)	<0.001	<0.001	<0.001	0.001	<0.001
EPIC urinary	95.2 (0.9)	78.7 (1.6)	83.2 (1.5)	88.5 (1.2)	88.2 (1.3)	<0.001	<0.001	<0.001	<0.001	<0.001
EPIC bowel	98.5 (0.3)	97.2 (0.5)	96.8 (0.9)	97.4 (0.9)	97.9 (0.7)	0.215	—	—	—	—
EPIC sexual	59.4 (2.4)	24.4 (1.8)	23.7 (1.6)	33.8 (2.1)	33.1 (2.1)	<0.001	<0.001	<0.001	<0.001	<0.001
EPIC hormonal	93.5 (1.0)	92.9 (1.0)	93.4 (1.0)	93.3 (1.0)	93.7 (1.0)	0.713	—	—	—	—
AUA-7	6.1 (0.6)	8.4 (0.6)	6.5 (0.6)	4.7 (0.5)	4.9 (0.6)	<0.001	0.012	1.0	0.167	0.591

Abbreviation: ANOVA = analysis of variance. Other abbreviations as in Table 1.

\* Bonferroni adjustment for multiple comparisons.

a total of 120 patients would be required in each treatment group to detect a 5-point change on the EPIC urinary irritation score (in which small to moderate between-group differences were expected) given an SD of 18.5 (37) and a statistical power of at least 80% at a significance level of 5%, with an expected loss to follow-up of 10%.

### Statistical analysis

The analyst was blinded to treatment assignment. Differences in patient characteristics and HRQL scores between treatment groups were tested with  $\chi^2$  tests and one-way analysis of variance, depending on the nature of the variables. We used the Tukey studentized range (honestly significant difference) test for *post hoc* comparisons among group means.

To assess within-group changes in HRQL, univariate repeated-measures analysis of variance was conducted using the summary scores of the different questionnaires. Pairwise comparisons between evaluations were made using the paired *t* test with the Bonferroni method to adjust for multiple comparisons. Figures showing the evolution of HRQL dimension scores during follow-up were constructed for each treatment group.

To test for differences in HRQL scores after 2 years of follow-up (1) unpaired *t* tests were used to compare low-risk and intermediate/high-risk groups, (2) one-way analysis of variance was used to compare HRQL scores between the three treatment groups, and (3)

generalized estimating equations (GEE) models were used to assess differences by treatment group after adjusting for pretreatment score, age at diagnosis, risk group, and hormonal treatment. These models, which took into account clustering of outcomes by surgeon or radiation oncologist, were constructed using SUDAAN version 9.0 (Research Triangle Institute, Research Triangle Park, NC) (41).

## RESULTS

We recruited a total of 841 patients, of whom 44 were excluded because they did not meet the inclusion criteria. A further 18 patients transferred to other hospitals before treatment, and 14 refused to participate. Of the 765 patients included in the study, 72 refused to complete the HRQL interviews, and the pretreatment interview was not performed in 79 patients owing to technical problems, particularly owing to delays in communicating data to the coordinating center. A total of 614 patients were included in the HRQL study presented here. Of these, 134 were treated with radical prostatectomy, 205 with external conformal radiotherapy, and 275 with prostate brachytherapy.

Table 1 shows patient clinical characteristics by treatment group at baseline. Statistically significant differences were

Table 3. Repeated-measures analysis of variance of quality-of-life measures for men treated with three-dimensional conformal radiotherapy

Quality of life measure	Mean (SE)					<i>p</i> (ANOVA)	<i>p</i> (vs. pretreatment)*			
	Pretreatment	Month 3	Month 6	Month 12	Month 24		Month 3	Month 6	Month 12	Month 24
SF-36 PCS	52.5 (0.5)	51.4 (0.5)	51.0 (0.4)	50.9 (0.5)	49.2 (0.6)	<0.001	0.089	0.012	0.007	<0.001
SF-36 MCS	54.9 (0.5)	55.3 (0.6)	55.9 (0.5)	56.3 (0.5)	56.3 (0.5)	0.015	1.0	0.558	0.039	0.080
FACT-G	80.0 (0.8)	80.2 (0.9)	80.4 (0.9)	80.6 (0.9)	77.5 (0.9)	0.008	1.0	1.0	1.0	0.007
FACT-P	38.9 (0.4)	38.1 (0.4)	38.7 (0.3)	38.7 (0.4)	37.5 (0.4)	0.012	0.225	1.0	1.0	0.001
EPIC urinary	96.4 (0.5)	92.2 (0.9)	96.1 (0.7)	94.7 (0.8)	94.2 (0.8)	0.006	<0.001	1.0	0.410	0.047
EPIC bowel	97.1 (0.4)	93.8 (0.9)	93.9 (1.0)	94.6 (0.8)	94.5 (0.9)	0.046	0.001	0.007	0.033	0.016
EPIC sexual	50.2 (2.0)	42.9 (1.9)	45.5 (2.0)	44.1 (1.9)	43.5 (1.9)	0.029	0.004	0.263	0.031	0.018
EPIC hormonal	93.9 (0.8)	90.7 (1.0)	91.9 (1.0)	92.9 (0.8)	93.7 (0.9)	0.024	0.002	0.387	1.0	1.0
AUA-7	6.6 (0.5)	8.8 (0.6)	5.9 (0.5)	5.4 (0.4)	6.4 (0.5)	<0.001	0.001	1.0	0.126	1.0

Abbreviations as in Tables 1 and 2.

\* Bonferroni adjustment for multiple comparisons.

Table 4. Repeated-measures analysis of variance of quality-of-life measures for men treated with brachytherapy

Quality of life measure	Mean (SE)					<i>p</i> (ANOVA)	<i>p</i> (vs. pretreatment)*			
	Pretreatment	Month 3	Month 6	Month 12	Month 24		Month 3	Month 6	Month 12	Month 24
SF-36 PCS	54.0 (0.4)	53.1 (0.3)	52.4 (0.4)	52.2 (0.4)	50.9 (0.5)	<0.001	0.070	0.001	<0.001	<0.001
SF-36 MCS	54.3 (0.4)	54.7 (0.5)	55.7 (0.4)	56.5 (0.4)	56.3 (0.4)	0.004	1.0	0.016	<0.001	0.002
FACT-G	80.4 (0.6)	81.0 (0.6)	81.1 (0.6)	82.5 (0.6)	79.8 (0.6)	0.018	1.0	1.0	0.018	1.0
FACT-P	39.4 (0.3)	38.1 (0.3)	38.7 (0.3)	39.5 (0.3)	38.9 (0.3)	0.005	<0.001	0.115	1.0	0.663
EPIC urinary	95.2 (0.6)	85.0 (1.0)	89.5 (0.9)	92.6 (0.8)	92.4 (0.8)	<0.001	<0.001	<0.001	0.014	0.005
EPIC bowel	96.9 (0.4)	95.3 (0.6)	95.2 (0.6)	96.8 (0.6)	97.9 (0.3)	0.008	0.072	0.107	1.0	0.263
EPIC sexual	48.6 (1.7)	46.3 (1.7)	47.1 (1.7)	50.5 (1.6)	49.8 (1.6)	0.100	—	—	—	—
EPIC hormonal	93.4 (0.7)	92.8 (0.7)	94.3 (0.6)	95.5 (0.5)	95.5 (0.5)	0.009	1.0	1.0	0.016	0.051
AUA-7	5.7 (0.4)	12.8 (0.5)	8.9 (0.4)	5.7 (0.4)	5.7 (0.4)	<0.001	<0.001	<0.001	1.0	1.0

Abbreviations as in Tables 1 and 2.

\* Bonferroni adjustment for multiple comparisons.

observed between the three treatment groups on all clinical variables. Patients treated with external radiotherapy had a mean PSA value of 10.1 ng/mL, which was significantly higher than in the other two treatment groups. There were statistically significant differences between the prostatectomy and brachytherapy groups in terms of Gleason score (6.8 vs. 5.7;  $p = 0.042$ ), and there was a significantly higher percentage of clinical stage T1 patients in the brachytherapy group (81.5%) compared with the surgery and external radiotherapy groups (65.7% and 51.7%, respectively). The

percentage of low-risk patients in the brachytherapy group was also much higher.

Neoadjuvant hormonal therapy before definitive treatment was less frequent in the surgery group (8.2%) than in the external radiotherapy and brachytherapy groups (33.7% and 31.6%, respectively). In patients receiving neoadjuvant hormonal therapy, the most frequently used treatment was a combination of an antiandrogen and a luteinizing hormone-releasing hormone (LHRH) analogue (86.2%); 10.8% were treated with an antiandrogen, and 3.0% with

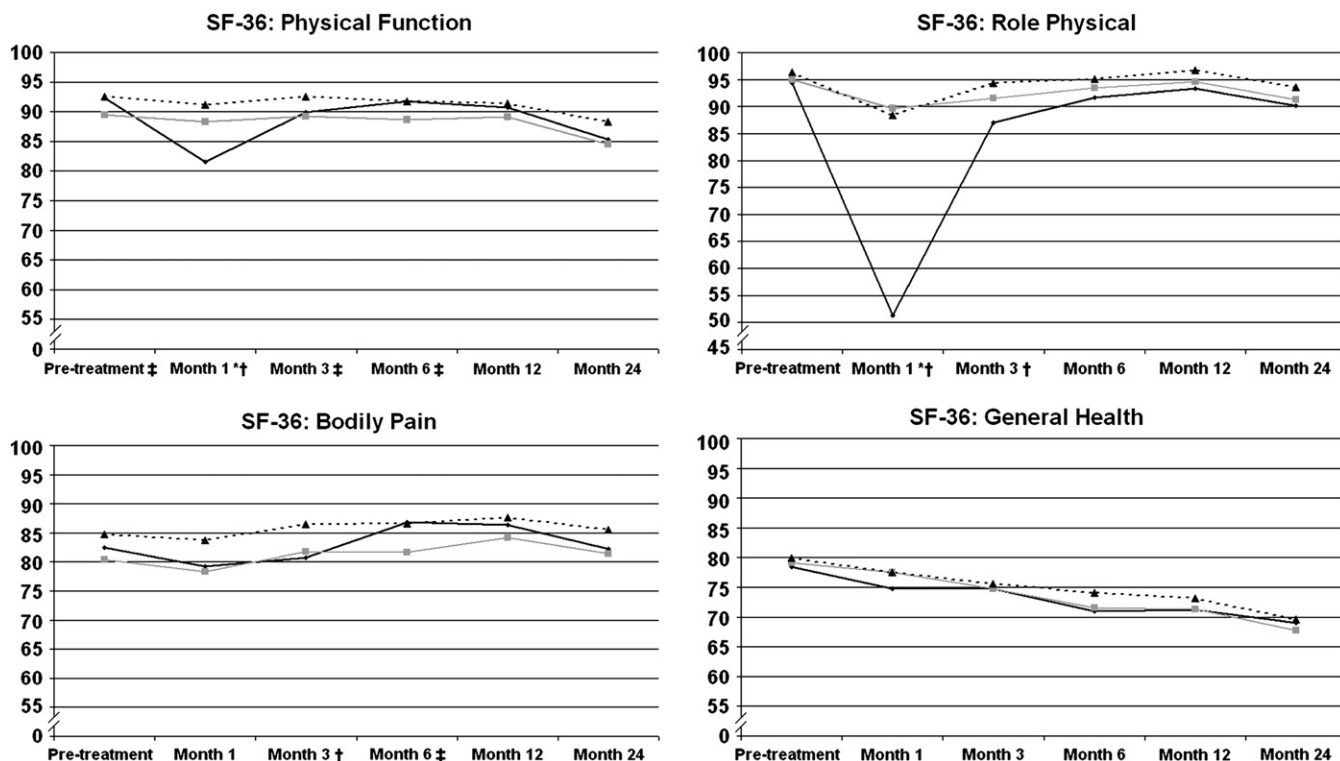


Fig. 1. Means of Medical Outcomes Study 36-Item Short Form (SF-36) dimension scores forming the physical component by treatment group: radical prostatectomy (solid black line), brachytherapy (dotted black line), and three-dimensional (3D) external beam radiotherapy (solid grey line). One-way analysis of variance to compare scores among the three treatment groups; Tukey studentized range (honestly significant difference) *post hoc* comparisons with  $p < 0.05$  for: \*radical prostatectomy vs. 3D conformal radiotherapy; †radical prostatectomy vs. brachytherapy; and ‡brachytherapy vs. 3D conformal radiotherapy.

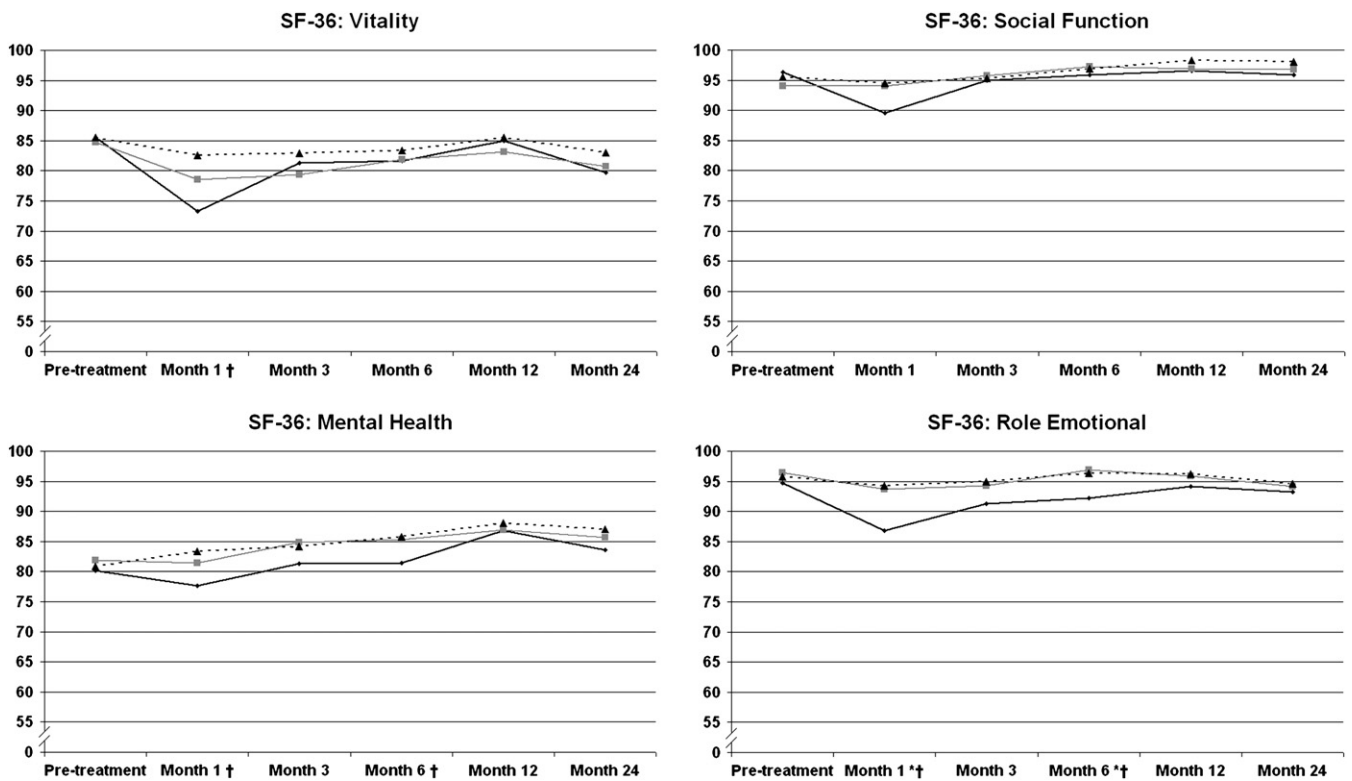


Fig. 2. Means of Medical Outcomes Study 36-Item Short Form (SF-36) dimension scores forming the mental component by treatment group: radical prostatectomy (solid black line), brachytherapy (dotted black line), and three-dimensional (3D) external beam radiotherapy (solid grey line). One-way analysis of variance to compare scores among the three treatment groups; Tukey studentized range (honestly significant difference) *post hoc* comparisons with  $p < 0.05$  for: \*radical prostatectomy vs. 3D conformal radiotherapy; †radical prostatectomy vs. brachytherapy; and ‡brachytherapy vs. 3D conformal radiotherapy.

an LHRH analogue. During follow-up, treatment for erectile dysfunction was prescribed to 52 patients (15.7% in the prostatectomy group, 5.4% in the external radiotherapy group, and 7.3% in the brachytherapy group;  $p = 0.002$ ). Phosphodiesterase type 5 inhibitors were the most frequently prescribed treatment (82.7% of these patients).

At the pretreatment evaluation, there were no statistically significant differences among the three treatment groups on the majority of the HRQL measures. The only exceptions were the SF-36 PCS and the EPIC sexual summary (Table 1). Brachytherapy patients had significantly higher (better) scores than external conformational radiotherapy on the SF-36 PCS (53.8 vs. 52.3), whereas radical prostatectomy patients had higher (better) scores than external conformal radiotherapy and brachytherapy patients on the EPIC sexual summary score (58.2 vs. 49.1 and 48.5, respectively). Response rates to the HRQL interviews were greater than 87% in all follow-up evaluations, except at Month 1. No differences in response rates were observed between treatment groups. The response rate to the HRQL interview at Month 1 was lower (49.5%) because scheduled evaluations at Months 1 and 3 meant a high concentration of HRQL interviews in a relatively short period of time, and we prioritized the evaluation at Month 3. For this reason the HRQL evaluation at Month 1 was not included in the univariate repeated-measures analysis.

Table 2 shows the pre- and posttreatment HRQL scores of patients who received retropubic radical prostatectomy. Deterioration in HRQL scores after treatment was observed on the SF-36 PCS, the FACT-P, the EPIC urinary and sexual summary scores, and the AUA-7. Compared with the pretreatment evaluation, the SF-36 PCS showed significant differences at 3 months and 2 years ( $p = 0.001$  and  $p < 0.001$ ). The specific questionnaires showed that surgery has the greatest impact on sexual and urinary function and bother scores at Months 3 and 6 after treatment. A partial recovery was observed after 1 year, although the differences with pretreatment scores were still significant 2 years from baseline (except on the AUA-7).

In patients who received 3D conformal radiation therapy, FACT and SF-36 scores were relatively stable in the evaluations after treatment (Table 3). Over the full 2 years of follow-up, however, there was a slight but sustained deterioration in HRQL, and at 2 years, scores on both questionnaires were significantly lower than those before treatment. The only exception was the SF-36 MCS, which showed some improvement. The four EPIC summary scores showed the impact of external radiotherapy 3 months after treatment. With the exception of the bowel domain, patient scores returned to the pretreatment level 6 months after treatment, though this was followed by a slight deterioration in HRQL. Finally, after 2 years scores were again significantly lower than at baseline in the urinary, bowel, and sexual domains.

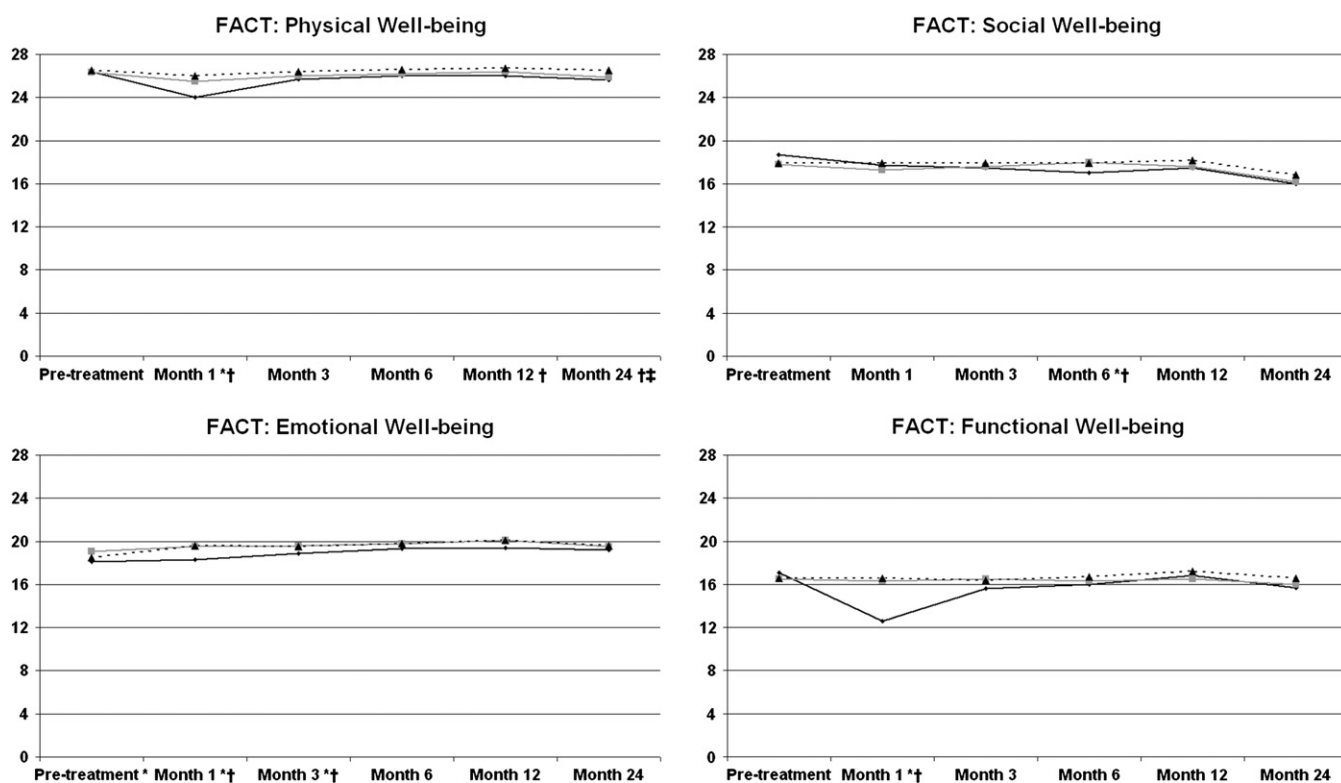


Fig. 3. Means of Functional Assessment of Cancer Therapy–General (FACT) dimension scores by treatment group: radical prostatectomy (solid black line), brachytherapy (dotted black line), and three-dimensional (3D) external beam radiotherapy (solid grey line). One-way analysis of variance to compare scores among the three treatment groups; Tukey studentized range (honestly significant difference) *post hoc* comparisons with  $p < 0.05$  for: \*radical prostatectomy vs. 3D conformal radiotherapy; †radical prostatectomy vs. brachytherapy; and ‡brachytherapy vs. 3D conformal radiotherapy.

Table 4 shows pre- and posttreatment scores on the HRQL questionnaires for patients treated with prostate brachytherapy. In general, scores on the generic questionnaires (SF-36 and FACT) remained quite stable, with only the SF-36 PCS showing a statistically significant decrease from baseline. The specific questionnaires showed that maximum impact on urinary function with prostate brachytherapy occurred in the third month after treatment, though by Month 6 there had been a partial recovery. Differences with respect to the pretreatment score were nevertheless significant in all evaluations.

Figure 1 shows the evolution in mean scores over the duration of the study period for the four SF-36 dimensions, which contribute most to the physical component of health. The impact of surgery was greatest over the short term, and patients recovered their previous level of health after 6 months. Similar results were noted for all three treatment groups from Month 6 to 2 years. Surgery had a much smaller impact on the dimensions of mental health, as shown in Fig. 2. The four dimensions of the FACT general module show a similar pattern to the SF-36 (Fig. 3). Figure 4 shows that prostatectomy had a considerably greater effect on the urinary incontinence and sexual subscales of the EPIC questionnaire than the other two treatments.

Table 5 shows HRQL scores after 2 years of follow-up by treatment and risk group. There were no differences in HRQL scores between patients with a low vs. intermediate/high risk

of prostate cancer in any of the treatment groups. In the comparison of the three treatment groups at 2 years from baseline (right-most column of Table 5), statistically significant differences were observed on all HRQL endpoints except the PCS, MCS, AUA-7, and EPIC hormonal. Patients who underwent prostatectomy had significantly lower (worse) scores on both the FACT-G and the FACT-P than patients treated with brachytherapy. *Post hoc* analysis of the EPIC urinary domain also showed that urinary summary and urinary incontinence scores were significantly worse in the radical prostatectomy group compared with the other two groups (77.0 vs. 94.1 and 92.5;  $p < 0.001$  in both *post hoc* contrasts for the urinary incontinence), though the same patients had significantly better scores than those treated with brachytherapy on the urinary irritation score (96.3 vs. 92.5;  $p = 0.004$ ). The external radiotherapy group had the worst scores on the bowel summary (94.6 vs. 98.1 and 97.8;  $p < 0.001$  in both *post hoc* comparisons), whereas on the sexual summary score the brachytherapy group had the best score (mean of 49.8) and the prostatectomy group had the worst score (mean of 32.5). The external radiotherapy group was between the two (mean of 43.6).

The GEE models (Table 6) also showed that risk group was not associated with EPIC scores after 2 years of follow-up. Neoadjuvant hormonal therapy only showed statistically significant association with the EPIC sexual summary

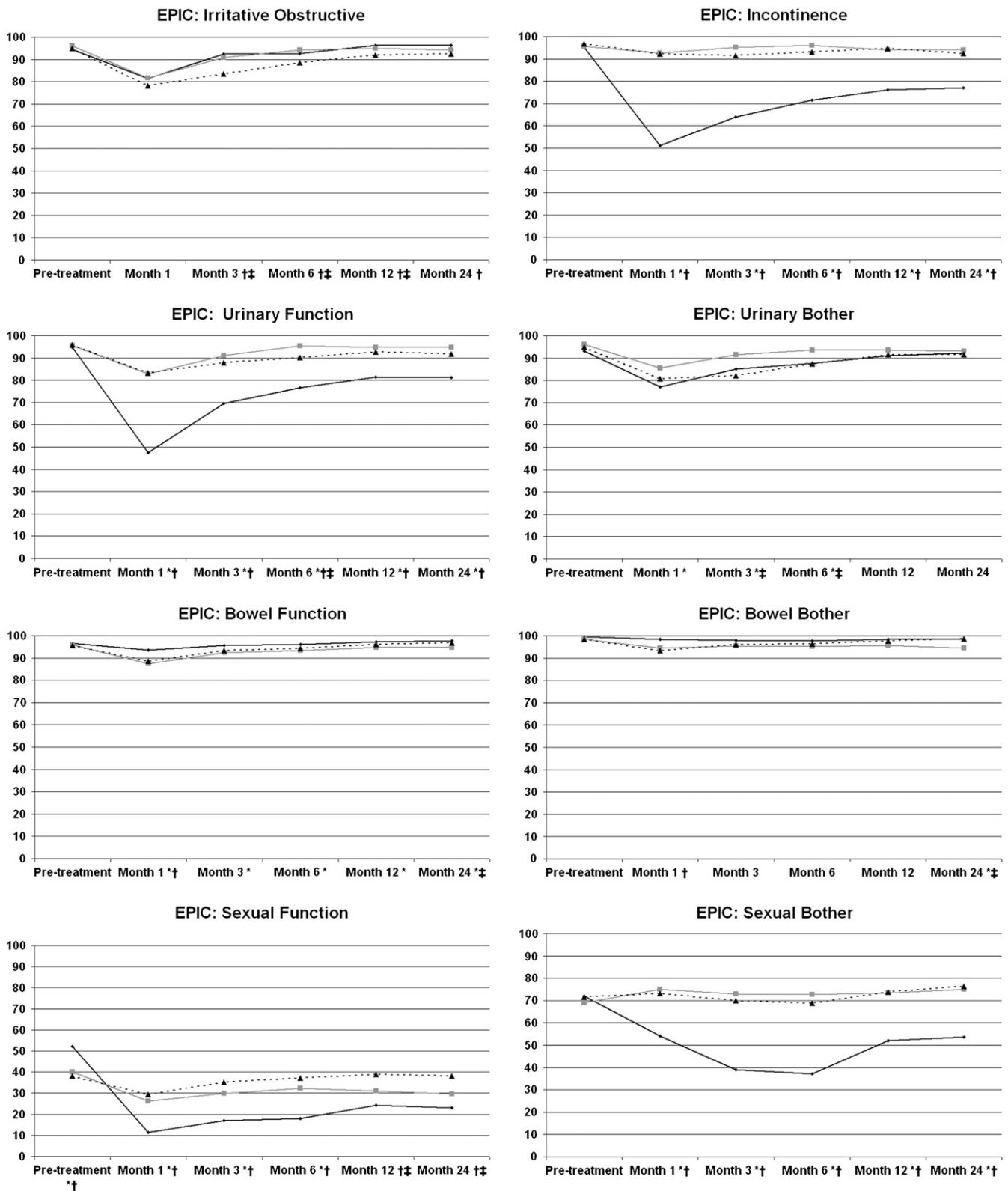


Fig. 4. Means of Expanded Prostate Cancer Index Composite (EPIC) subscale scores by treatment group: radical prostatectomy (solid black line), brachytherapy (dotted black line), and three-dimensional (3D) external beam radiotherapy (solid grey line). One-way analysis of variance to compare scores among the three treatment groups; Tukey studentized range (honestly significant difference) *post hoc* comparisons with  $p < 0.05$  for: \*radical prostatectomy vs. 3D conformal radiotherapy; †radical prostatectomy vs. brachytherapy; and ‡brachytherapy vs. 3D conformal radiotherapy.

Table 5. HRQL scores by treatment and risk group at 2-year follow-up

Quality of life measure	Radical prostatectomy			3D conformal radiotherapy			Brachytherapy			<i>p</i> *
	Low risk	Intermediate or high risk	<i>p</i>	Low risk	Intermediate or high risk	<i>p</i>	Low risk	Intermediate or high risk	<i>p</i>	
SF-36 PCS	50.4 (7.5)	49.7 (7.5)	0.608	48.9 (7.2)	49.9 (6.9)	0.356	51.1 (6.8)	49.1 (5.9)	0.123	0.094
SF-36 MCS	55.1 (8.1)	55.2 (6.7)	0.950	56.1 (6.4)	56.0 (6.4)	0.956	55.9 (6.9)	58.2 (3.9)	0.077	0.373
FACT-G	76.8 (9.4)	76.2 (9.5)	0.744	76.7 (11.1)	78.4 (9.3)	0.263	79.5 (9.3)	79.9 (6.2)	0.824	0.008 <sup>‡</sup>
FACT-P	36.9 (4.8)	37.3 (4.4)	0.644	37.6 (4.9)	37.7 (4.9)	0.934	38.9 (4.2)	38.4 (3.6)	0.577	0.001 <sup>‡§</sup>
AUA-7	5.9 (6.2)	4.8 (5.3)	0.292	5.38 (5.2)	6.7 (6.3)	0.143	5.83 (5.3)	6.7 (6.8)	0.456	0.405
EPIC urinary	87.7 (13.8)	87.3 (13.1)	0.863	94.0 (11.2)	92.7 (11.3)	0.441	91.9 (11.6)	90.2 (12.5)	0.466	<0.001 <sup>††</sup>
Urinary irritative	96.4 (10.3)	96.2 (8.2)	0.923	94.8 (10.1)	93.8 (10.4)	0.523	92.7 (10.8)	91.1 (12.0)	0.445	0.005 <sup>‡</sup>
Urinary incontinence	78.3 (23.1)	76.3 (22.0)	0.659	93.2 (13.9)	94.9 (11.6)	0.367	92.7 (15.2)	90.7 (18.3)	0.507	<0.001 <sup>††</sup>
EPIC bowel	98.9 (2.3)	97.6 (7.6)	0.233	94.1 (11.2)	95.0 (9.7)	0.574	97.7 (6.0)	97.8 (4.4)	0.922	<0.001 <sup>†§</sup>
EPIC sexual	33.0 (21.6)	32.1 (19.9)	0.824	42.2 (22.5)	44.9 (24.4)	0.437	50.5 (23.9)	45.0 (22.1)	0.250	<0.001 <sup>†‡§</sup>
EPIC hormonal	94.0 (8.6)	93.8 (9.9)	0.900	94.3 (11.4)	93.0 (11.2)	0.455	95.6 (7.3)	95.1 (5.9)	0.718	0.074

Abbreviations as in Table 1.

\*One-way analysis of variance comparing HRQL scores among the three treatment groups; Tukey studentized range (honestly significant) *post hoc* comparisons with  $p < 0.05$  for <sup>†</sup>radical prostatectomy vs. three-dimensional (3D) conformal radiotherapy; <sup>‡</sup>radical prostatectomy vs. brachytherapy; and <sup>§</sup>brachytherapy vs. 3D conformal radiotherapy.

score. Patients who underwent retropubic radical prostatectomy had significantly worse results than those treated with brachytherapy on the sexual summary score ( $\beta$  coefficient =  $-20.37$ ;  $p < 0.001$ ) and on the urinary incontinence score ( $\beta$  coefficient =  $-14.07$ ;  $p < 0.001$ ). Patients treated with conformal external radiotherapy had significantly worse results than the brachytherapy group on the bowel, sexual, and hormonal summary scores ( $\beta$  coefficients =  $-3.55$ ,  $-5.24$ , and  $-1.94$ , respectively), but the prostatectomy group presented significantly higher (better) scores than the brachytherapy group in terms of urinary irritation ( $\beta$  coefficient =  $+4.16$ ;  $p < 0.001$ ).

## DISCUSSION

This comparative study of patients receiving one of three established treatments for localized prostate cancer has shown that differences between treatments on measures of generic HRQL were short-lived, but that relevant differences persisted between groups until 2 years after treatment on measures of sexual, urinary and bowel dysfunction.

The magnitude or clinical importance of the differences between the groups was interpreted using the standard categorization of effect size (42), whereby 0.2, 0.5, and 0.8 of the SD represent small, moderate, and large differences, respectively. First, at 2 years after treatment, patients in the prostatectomy group scored 20 points lower than patients in the brachytherapy group on the EPIC sexual summary score, and external radiation patients scored 5 points lower ( $\beta$  coefficients for the prostatectomy and radiation therapy groups were  $-20.37$  and  $-5.24$ , respectively). Given a baseline SD on the EPIC sexual summary score of 24, the effect size was large for prostatectomy (0.85) and small for external radiation (0.22). Second, the adjusted difference of  $-14.07$  points on the urinary incontinence scale for patients treated with prostatectomy compared with brachytherapy corresponded to a large effect size (1.03), when taking into

account an SD of 13.7 at the baseline visit. Third, brachytherapy showed a poorer outcome on the urinary irritation score than prostatectomy, with a statistically significant adjusted difference in the GEE model of 4.16, indicating a moderate effect (0.43). Finally, the adjusted difference of  $-3.55$  points reflected the moderate, negative impact of 3D conformal radiation therapy on bowel function and bother compared with brachytherapy (effect size of 0.58 with an SD of 6.1).

The questionnaires selected for the HRQL evaluation included the most widely used questionnaires in patients with localized prostate cancer and permit comparisons with other studies. The negative impact of 3D conformational radiotherapy on the EPIC bowel domain and the fact that brachytherapy fared more poorly on the scale measuring urinary irritation are consistent with the growing body of literature (20,43) in these patients. However, a study by Wei *et al.* (19) showed no differences in sexual summary scores and urinary incontinence scores between patients treated with radical prostatectomy and brachytherapy. Nevertheless, findings from our study are similar to those from the first recent study to compare modern approaches to monotherapy (44) and indicate the extent to which radical prostatectomy negatively impacts sexual function and urinary continence.

Nerve-sparing techniques applied during radical prostatectomy may help to preserve sexual functioning. In our study, however, these techniques were not widely used (21% bilateral, 5% unilateral, and non-nerve-sparing in 74% of patients). Nevertheless, the EPIC sexual summary mean score in the radical prostatectomy group 2 years after treatment was 33.4 (95% confidence interval [CI] 29.0–36.5), which is very similar to the mean of 33.9 (95% CI 29.6–38.1) observed in the Wei *et al.* study (19), in which nerve-sparing techniques were applied in a much higher proportion (79%) of patients (20). Differences with respect to the Wei *et al.* study can be explained by the poorer outcomes observed in that study on the sexual functioning domain in the

Table 6. Association of clinical variables with EPIC scores 2 years after treatment using generalized estimating equations models

Variable	EPIC urinary irritative			EPIC urinary incontinence			EPIC bowel			EPIC sexual			EPIC hormonal		
	$\beta$	(SE)	<i>p</i>	$\beta$	(SE)	<i>p</i>	$\beta$	(SE)	<i>p</i>	$\beta$	(SE)	<i>p</i>	$\beta$	(SE)	<i>p</i>
Intercept	71.05	(8.21)	<0.001*	75.75	(9.50)	<0.001*	53.57	(10.9)	<0.001*	66.10	(18.20)	<0.001*	62.25	(9.63)	<0.001*
Pretreatment score	0.27	(0.05)	<0.001*	0.26	(0.05)	<0.001*	0.41	(0.10)	<0.001*	0.36	(0.04)	<0.001*	0.30	(0.09)	0.01*
Age	-0.06	(0.10)	0.56	-0.11	(0.11)	0.35	0.06	(0.06)	0.30	-0.44	(0.27)	0.11	0.09	(0.05)	0.11
Risk group															
Intermediate/high	(reference)			(reference)			(reference)			(reference)			(reference)		
Low	1.03	(0.86)	0.25	0.54	(1.66)	0.75	-0.57	(0.73)	0.45	0.55	(1.91)	0.78	1.02	(0.55)	0.08
Hormonal treatment															
Yes	(reference)			(reference)			(reference)			(reference)			(reference)		
No	-0.81	(1.11)	0.48	-2.14	(1.39)	0.14	1.34	(0.72)	0.08	-6.51	(2.77)	0.03*	-1.68	(1.10)	0.15
Group of treatment															
Brachytherapy	(reference)			(reference)			(reference)			(reference)			(reference)		
Prostatectomy	4.16	(0.90)	<0.001*	-14.07	(1.94)	<0.001*	-0.52	(0.48)	0.30	-20.37	(1.70)	<0.001*	-0.75	(0.60)	0.23
3D conformal radiotherapy	2.30	(1.28)	0.09	2.03	(1.37)	0.16	-3.55	(1.05)	<0.001*	-5.24	(1.91)	0.01*	-1.94	(0.61)	0.01*

Abbreviations as in Table 1.

\* *p* < 0.05.

brachytherapy group. It was argued that those results were likely due, among other factors, to the combination of brachytherapy and external beam radiotherapy (44) and the extensive use of adjuvant or neoadjuvant hormone therapy (51% of patients). In our study, better scores were also observed on the EPIC hormonal summary; which is likely because only neoadjuvant hormone therapy was applied.

The utility of the risk groups defined according to pretreatment PSA level, biopsy Gleason score, and T stage in predicting biochemical outcome after treatment has been well described (13, 16). It is therefore important to control for these known predictive factors when comparing results between treatments. However, no differences in HRQL were observed between low- and intermediate/high-risk groups at 2 years after treatment in any of the treatment groups by bivariate analysis. The GEE models constructed with the EPIC summary scores confirmed this finding. The adjusted differences between low- and intermediate/high-risk localized prostate cancer patients 2 years after the treatment were small (range, 0.45–1.03 points) and not statistically significant in any of the models. In the present study, intermediate- and high-risk patients were aggregated into one category because of the low proportion of high-risk patients, which ranged from 0.7% in the brachytherapy group to 18.0% in the external radiotherapy group. For this reason these results are not generalizable to high-risk patients with localized prostate cancer, and further research is needed to assess whether HRQL in this group differs from that in low- or intermediate-risk patients.

Two advantages of the present study with respect to earlier studies were the inclusion of a pretreatment evaluation, which allowed for a valid comparison between treatment options, and repeated follow-up measurements. Previous studies that compared treatments and incorporated a pretreatment evaluation used only small sample sizes and were limited to 1 year of follow-up (26–28). Longer-term studies with large samples by treatment have been cross-sectional in nature (19–21, 23–25,44). Furthermore, we ensured that HRQL evaluation was homogeneous for all study subjects, independently of the center where they were recruited and treated, by using centralized telephone interviews performed by two trained interviewers.

Study limitations include the fact that participants were not randomized to the different treatment groups. Randomization would probably have avoided the differences in clinical characteristics seen among the treatment groups at baseline, although, interestingly, there were no notable differences on pretreatment quality of life scores between groups. Likewise, the results of the GEE models that allowed to us to adjust for pretreatment differences on the main prognostic variables are consistent with the results obtained from bivariate comparisons of the treatment groups. Finally, response rates were higher than 87% in all follow-up evaluations and treatment groups, except for Month 1. Specifically, response rate at 2 years after treatment was 91.0%, 87.3%, and 87.3% among prostatectomy, external radiotherapy, and brachytherapy groups, respectively.

In conclusion, our study allowed for both the short- and long-term assessment of patient outcomes associated with three treatments for localized prostate cancer. Radical prostatectomy was found to have a considerable negative effect on sexual functioning and urinary continence, whereas 3D conformal radiotherapy had a moderate negative effect

on bowel functioning and a small negative effect on sexual functioning. The only negative outcome associated with brachytherapy was a moderate increase in urinary irritation. These results will provide both patients and professionals with relevant information for shared clinical decision making.

## REFERENCES

- Sant M, Aareleid T, Berrino F, *et al.* EUROCARE-3: Survival of cancer patients diagnosed 1990-94—Results and commentary. *Ann Oncol* 2003;14(Suppl. 5):v61-v118.
- Morote-Robles J. [Is the era of prostatic specific antigen over?]. *Med Clin (Barc)* 2006;126:579-580.
- Catalona WJ, Richie JP, Ahmann FR, *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151:1283-1290.
- Morote J, Raventos CX, Lorente JA, *et al.* Measurement of free PSA in the diagnosis and staging of prostate cancer. *Int J Cancer* 1997;71:756-759.
- Morote J. La cuantificación de la isoforma compleja del antígeno prostático específico (PSAc). Un nuevo reto en la era del PSA. *Med Clin (Barc)* 2004;122:241-244.
- Catalona WJ, Loeb S. The PSA era is not over for prostate cancer. *Eur Urol* 2005;48:541-545.
- Ochiai A, Babaian RJ. Update on prostate biopsy technique. *Curr Opin Urol* 2004;14:157-162.
- Catalona W, Yu X, Roehl R, *et al.* Serum PSA correlates more strongly with percentage of cancer and cancer volume than with prostate size. *J Urol* 2005;173:257.
- Pound CR, Partin AW, Eisenberger MA, *et al.* Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-1597.
- Kupelian PA, Katcher J, Levin HS, *et al.* Stage T1-2 prostate cancer: A multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. *Int J Radiat Oncol Biol Phys* 1997;37:1043-1052.
- Trapasso JG, deKernion JB, Smith RB, *et al.* The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. *J Urol* 1994;152:1821-1825.
- Kupelian P, Katcher J, Levin H, *et al.* Correlation of clinical and pathologic factors with rising prostate-specific antigen profiles after radical prostatectomy alone for clinically localized prostate cancer. *Urology* 1996;48:249-260.
- 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.
- Polascik TJ, Pound CR, DeWeese TL, *et al.* Comparison of radical prostatectomy and iodine 125 interstitial radiotherapy for the treatment of clinically localized prostate cancer: A 7-year biochemical (PSA) progression analysis. *Urology* 1998;51:884-889.
- Ramos CG, Carvalhal GF, Smith DS, *et al.* Retrospective comparison of radical retropubic prostatectomy and 125iodine brachytherapy for localized prostate cancer. *J Urol* 1999;161:1212-1215.
- Stokes SH. Comparison of biochemical disease-free survival of patients with localized carcinoma of the prostate undergoing radical prostatectomy, transperineal ultrasound-guided radioactive seed implantation, or definitive external beam irradiation. *Int J Radiat Oncol Biol Phys* 2000;47:129-136.
- Oliva G. Braquiteràpia en el Càncer de Pròstata. Barcelona: Agencia Avaluacio Tecnologia Medica; 2000. p. 1-59.
- Conseil d'évaluation des technologies de la santé du Québec (CETS). Brachytherapy and Prostate Cancer. Québec: Les Publications du Québec; 2000.
- Wei JT, Dunn RL, Sandler HM, *et al.* Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. *J Clin Oncol* 2002;20:557-566.
- Miller DC, Sanda MG, Dunn RL, *et al.* Long-term outcomes among localized prostate cancer survivors: Health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol* 2005;23:2772-2780.
- Davis JW, Kuban DA, Lynch DF, *et al.* Quality of life after treatment for localized prostate cancer: Differences based on treatment modality. *J Urol* 2001;166:947-952.
- Krupski T, Petroni GR, Bissonette EA, *et al.* Quality-of-life comparison of radical prostatectomy and interstitial brachytherapy in the treatment of clinically localized prostate cancer. *Urology* 2000;55:736-742.
- Namiki S, Tochigi T, Kuwahara M, *et al.* Health related quality of life in Japanese men after radical prostatectomy or radiation therapy for localized prostate cancer. *Int J Urol* 2004;11:619-627.
- Penson DF, Feng Z, Kuniyuki A, *et al.* General quality of life 2 years following treatment for prostate cancer: What influences outcomes? Results from the prostate cancer outcomes study. *J Clin Oncol* 2003;21:1147-1154.
- Smith DS, Carvalhal GF, Schneider K, *et al.* Quality-of-life outcomes for men with prostate carcinoma detected by screening. *Cancer* 2000;88:1454-1463.
- Borchers H, Kirschner-Hermanns R, Brehmer B, *et al.* Permanent 125I-seed brachytherapy or radical prostatectomy: A prospective comparison considering oncological and quality of life results. *BJU Int* 2004;94:805-811.
- Schapira MM, Lawrence WF, Katz DA, *et al.* Effect of treatment on quality of life among men with clinically localized prostate cancer. *Med Care* 2001;39:243-253.
- Lee WR, Hall MC, McQuellon RP, *et al.* A prospective quality-of-life study in men with clinically localized prostate carcinoma treated with radical prostatectomy, external beam radiotherapy, or interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51:614-623.
- Green FL, Page DL, Fleming ID, *et al.* Prostate. In: Green FL, Page DL, Fleming ID, *et al.* AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; Prostate 2002. p. 347-356.
- Bice WS Jr., Prestidge BR, Prete JJ, *et al.* Clinical impact of implementing the recommendations of AAPM Task Group 43 on permanent prostate brachytherapy using 125I. American Association of Physicists in Medicine. *Int J Radiat Oncol Biol Phys* 1998;40:1237-1241.
- Alonso J, Prieto L, Anto JM. La versión española del "SF-36 Health Survey" (Cuestionario de Salud SF-36): Un instrumento para la medida de los resultados clínicos. *Med Clin (Barc)* 1995;104:771-776.
- Vilagut G, Ferrer M, Rajmil L, *et al.* El cuestionario de salud SF-36 español: Una década de experiencia y nuevos desarrollos. *Gac Sanit* 2005;19:135-150.

33. Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 health survey (standard and acute forms). Lincoln, RI: Quality Metric Incorporated; 2000.
34. Cella D, Hernandez L, Bonomi AE, *et al.* Spanish language translation and initial validation of the functional assessment of cancer therapy quality-of-life instrument. *Med Care* 1998; 36:1407–1418.
35. Esper P, Mo F, Chodak G, *et al.* Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997;50:920–928.
36. Batista Miranda JE, Sevilla-Cecilia C, Torrubia R, *et al.* Quality of life in prostate cancer and controls: Psychometric validation of the FACTP-4 Spanish, and relation to urinary symptoms. *Arch Esp Urol* 2003;56:447–454.
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. Litwin MS, Hays RD, Fink A, *et al.* The UCLA Prostate Cancer Index: Development, reliability, and validity of a health-related quality of life measure. *Med Care* 1998;36:1002–1012.
39. Badia X, Garcia-Losa M, Dal Re R, *et al.* Validation of a harmonized Spanish version of the IPSS: Evidence of equivalence with the original American scale. *International Prostate Symptom Score. Urology* 1998;52:614–620.
40. Badia X, Garcia-Losa M, Dal Re R. Ten-language translation and harmonization of the International Prostate Symptom Score: Developing a methodology for multinational clinical trials. *Eur Urol* 1997;31:129–140.
41. Research Triangle Institute. SUDAAN language manual, release 9.0. Research Triangle Park, NC: Research Triangle Institute; 2004.
42. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care* 1989;27:S178–S189.
43. Hollenbeck BK, Dunn RL, Wei JT, *et al.* Determinants of long-term sexual health outcome after radical prostatectomy measured by a validated instrument. *J Urol* 2003;169:1453–1457.
44. Frank SJ, Pisters LL, Davis J, *et al.* An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. *J Urol* 2007;177: 2151–2156.