

# Localized Prostate Cancer in Norway, the United States, and Spain: Between-Country Differences of Variables Before Treatment Among Patients Eligible for Curative Treatment

Anne Holck Storås,<sup>1</sup> Martin G. Sanda,<sup>2</sup> Montse Ferrer,<sup>3</sup>  
Jon Håvard Loge,<sup>1,4</sup> Alv A. Dahl,<sup>1,4</sup> Eivind A.S. Steinsvik,<sup>5</sup> Ferran Guedea,<sup>6</sup>  
Milada Cvancarova,<sup>1</sup> Sophie D. Fosså<sup>1,4</sup>

## Abstract

**Between-country differences in medical and sociodemographic variables, and patient-related outcomes (PROs) before treatment might explain published variations of side effects after radical prostatectomy (RP) or radiotherapy (RAD) for prostate cancer (PCa). This hypothesis was tested among 1908 patients from the United States, Spain, and Norway. Significant between-country differences were observed for most factors investigated before treatment. The observations should be considered in comparison of the frequency and severity of internationally published studies.**

**Background:** In men with PCa, large variations of PROs after RP or high-dose RAD might be related to between-country differences of medical and sociodemographic variables, and differences in PROs before treatment in the sexual and urinary domains. **Patients and Methods:** In 1908 patients with localized PCa from Norway, the United States, or Spain, the relation between medical (prostate-specific antigen, Gleason score, cT-category) and socio-demographic variables (age, education, marital status) before treatment was investigated. Using the Expanded Prostate Cancer Index Composite questionnaire, PROs before treatment within the sexual and urinary domains were also considered. **Results:** Compared with the European patients, American patients were younger, fewer had comorbid conditions, and more had a high education level. Fifty-three percent of the US men eligible for RP had low-risk tumors compared with 42% and 31% among the Norwegian and the Spanish patients, respectively. Among the Spanish RAD patients, 54% had had low-risk tumors compared with 34% of the American and 21% of the Norwegian men planned for RAD, respectively. Compared with the European patients, significantly fewer US patients reported moderate or severe sexual dysfunction and related problems. In most subgroups, the number of patients with sexual or urinary dysfunction exceeded that of patients with both related to the reported dysfunction. **Conclusion:** Statistically significant between-country differences were observed in medical and sociodemographic variables, and in PROs before treatment within the sexual and urinary domains. Large differences between reported dysfunction and related problems within the sexual and urinary domains indicate that dysfunction and bother should be reported separately in addition to calculation of summary scores. The documented differences, not at least regarding PROs, might in part explain the large variation of side effects after treatment evident in the medical literature.

*Clinical Genitourinary Cancer*, Vol. ■, No. ■, ■-■ © 2014 Elsevier Inc. All rights reserved.

**Keywords:** Between-country variables, Curative treatment, Prostate cancer, Radical prostatectomy, Radiotherapy

<sup>1</sup>Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway

<sup>2</sup>Department of Urology, Emory University Hospital, Atlanta, GA

<sup>3</sup>Health Services Research Group, IMIM (Hospital del Mar Research Institute), Barcelona, Spain

<sup>4</sup>Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>5</sup>Department of ENT, Division of Surgery, Akershus University Hospital, Lorenskog, Norway

<sup>6</sup>Department of Radiation Oncology, Catalan Institute of Oncology, L'Hospitalet de Llobregat, Barcelona, Spain

Submitted: Nov 12, 2013; Revised: Dec 30, 2013; Accepted: Dec 30, 2013

Address for correspondence: Sophie D. Fosså, MD, PhD, Oslo University Hospital, Radiumhospitalet, Postboks 4953, Nydalen, 0434 Oslo, Norway  
Fax: +41-22934553; e-mail contact: [sdf@ous-hf.no](mailto:sdf@ous-hf.no)

## Between-Country Differences Before Treatment in PCa

### Introduction

Standard curative treatment of prostate cancer (PCa) patients comprises radical prostatectomy (RP) and high-dose radiotherapy (RAD) with or without adjuvant androgen deprivation therapy (ADT). After adjustment for risk group allocation, PCa-specific survival appears to be similar after both treatment modalities.<sup>1-3</sup> However, the patterns of “typical adverse effects (AEs)” (dysfunction within the urinary, sexual, bowel, and hormonal domains and related problems) differ substantially.<sup>4,5</sup> Further, even though comparisons are restricted either to RP or RAD, large and generally unexplained variations of the frequency and severity of typical AEs are reported across studies and countries.<sup>6-10</sup> Such differences in patient-related outcomes (PROs) after treatment might affect the individual patient’s choice of RP versus RAD.

Except for different treatment techniques, variations of AEs after treatment might be related to differences in medical factors before treatment (tumor risk group allocation, comorbidity, general health condition) and sociodemographic factors (age, educational level, civil status). Some groups have documented some effect of PROs before treatment on AEs after RP or RAD.<sup>11,12</sup> However, the knowledge on between-country differences of PROs within the urinary and sexual domain is limited. Only Namiki et al have reported on differences of sexual function and bother in Japanese and American men before treatment.<sup>13</sup>

Our group has initiated a cohort study with research groups in the United States and Spain to perform between-country comparisons of variables before and after treatment and patient-reported typical AEs among patients treated with curative RP or RAD for PCa. The present article describes for each country, and separately for RP and RAD, medical and sociodemographic factors before treatment and PROs within the sexual, urinary, bowel, and hormonal domains. We also evaluated the correlation between patient-reported dysfunction and related problems. Finally, for each country we assessed the associations between factors before treatment and RP or RAD. We anticipated considerable between-country differences in the distribution of variables before treatment and the strength of their associations with the selected treatment. We also expected between-country differences in patient-reported treatment dysfunction and problems before treatment within the sexual and urinary domains.

### Patients and Methods

#### Study Design and Study Sites

This study represents a collaboration between Oslo University Hospital, Norway, the PROSTAQA (PRostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment) Study Group in Boston, MA, and The Spanish Group of Localized Prostate Cancer, Barcelona, Spain. Each group has published results regarding PROs before and after RP and RAD.<sup>14-18</sup> However, because the present study only included patients with clinically categorized T1 or T2 tumors, 28 RP and 80 RAD patients with T3/T4 tumors were excluded from the original Norwegian sample. In the Spanish sample, 10 RP and 65 RAD patients were excluded because of hormonal treatment before inclusion.

#### Patient Sampling

Eligible patients for the present study fulfilled the following criteria:

- Histologically confirmed PCa
- Clinical stage T1 or T2 tumor

- Known level of prostate-specific antigen (PSA) and Gleason score before treatment
- Planned RP or RAD
- No ADT before completion of the questionnaire before treatment

#### Treatment Techniques

Radical prostatectomy was performed using retropubic, laparoscopic, or robot-assisted techniques with or without nerve-sparing procedures. RAD ( $\geq 65$  Gy) was delivered as intensity modulated RAD, 3-D conformal technique, or a combination of high-dose brachytherapy and external beam RAD. Patients receiving low-dose brachytherapy alone were excluded because this option was not available in Norway.<sup>19</sup>

#### Clinical Variables

**Risk Groups.** Three risk groups were defined; low-risk: cT1-T2a and Gleason score 6 and PSA  $< 10$  ng/mL; intermediate-risk: cT2b-T2c or Gleason score 7 or PSA 10-20 ng/mL; and high-risk: Gleason score 8-10 and/or PSA  $> 20$  ng/mL.<sup>20</sup>

**Other Variables Assessed Before Treatment according to Patient Reports.** The level of education separated “less than high school” from “high school or more.” “Single” versus “paired relation” described the relationship status. Comorbidity was defined as the presence of at least 1 of 5 adverse health conditions: (1) diabetes; (2) heart failure and/or myocardial infarction and/or angina; (3) stroke; (4) ulcer and/or irritable bowel disease; and (5) asthma and/or bronchitis and/or breathing problems.

**Expanded PCa Index Composite.** Before treatment the patients completed a questionnaire containing a version of the Expanded Prostate Cancer Index Composite (EPIC) instrument. EPIC assesses patient-reported sexual, urinary, and bowel dysfunction and problems (“bother”)<sup>21</sup> and hormone treatment-related AEs.<sup>21,22</sup> The original questionnaire includes 50 items (EPIC-50) but was later abbreviated to 26 items (EPIC-26).<sup>22</sup> All questions in EPIC-26, completed by the American patients, are included in EPIC-50, used by the Norwegian and Spanish men. The present report is based on responses to items in EPIC-26.

Using 4- or 5-point Likert scales, the patient scored his function and related problems within each of the 4 domains (sexual, urinary, bowel and hormonal). The individual scores were then transformed into scales ranging from 0 to 100, with 0 representing maximum dysfunction/maximum problem and 100 indicating no dysfunction/no problem.<sup>23</sup> The scores within each domain were finally averaged. The resulting summary scores reflect functional aspects and problem experience within the sexual, urinary irritation/obstruction, urinary incontinence, bowel, or hormonal domains. Our patients’ answers to each of the 26 EPIC items were also dichotomized according to Sanda et al,<sup>16</sup> enabling separation patients with no/very small/small dysfunctions/problems (“absent dysfunction/problems”) from those with moderate/big dysfunctions/problems (“present dysfunction/problems”). In addition, we calculated mean scores for items which content addressed dysfunction as opposed to problem experience.

**Table 1** Demographic and Disease Characteristics of the Patients Before Treatment

Variable	Radical Prostatectomy					Radiotherapy				
	Norway (n = 627)	USA (n = 603)	Spain (n = 123)	P	Total (n = 1353)	Norway (n = 126)	USA (n = 293)	Spain (n = 126)	P	Total (n = 555)
<b>Age, Median (Range); &lt; 65 Years</b>	64 (44-78); 382 (61)	60 (39-80); 460 (76)	65 (45-75); 64 (52)	<.001 <sup>a,b</sup> ; <.001 <sup>a,b</sup>	62 (39-80); 906 (67)	67 (51-78); 41 (33)	69 (46-85); 86 (29)	70 (55-83); 25 (19)	≤.008 <sup>a,c</sup> ; .009 <sup>c</sup>	69 (46-85); 152 (27)
<b>No Comorbid Condition</b>	450 (72)	513 (85)	77 (63)	<.001 <sup>a,b</sup>	1040 (77)	64 (51)	200 (67)	77 (57)	<.001 <sup>a</sup>	341 (62)
<b>Paired Relationship</b>	584 (93)	523 (87)	109 (87)	<.001 <sup>a</sup>	1216 (90)	102 (83)	227 (78)	118 (87)	.018 <sup>b</sup>	447 (81)
<b>Education Greater Than High School Level</b>	322 (52)	511 (85)	8 (7)	<.001 <sup>a,b,c</sup>	841 (62)	57 (46)	211 (72)	16 (12)	<.001 <sup>a,b,c</sup>	284 (52)
<b>PSA, ng/mL</b>										
Median (Range)	8.2 (1.6-75)	5.5 (0.5-72)	7.4 (4-23)	≤.002 <sup>a,b,c</sup>	6.9 (0.5-75)	9.8 (3-87)	6.3 (0.5-99)	7.6 (1.2-38)	≤.009 <sup>a,b,c</sup>	7.6 (0.5-99)
<b>PSA Group</b>				<.001 <sup>a</sup>					<.001 <sup>a,c</sup>	
≤10.0	434 (69)	525 (87)	99 (81)		1058 (78)	66 (52)	226 (77)	114 (84)		406 (73)
>10-20	162 (26)	65 (11)	45 (15)		250 (18)	38 (30)	45 (15)	15 (11)		98 (18)
>20	31 (5)	13 (2)	1 (1)		45 (3)	22 (18)	22 (8)	7 (5)		51 (9)
<b>cT Category</b>				<.001 <sup>a</sup>					.005 <sup>a,c</sup>	
T1	393 (63)	437 (73)	82 (67)		912 (67)	53 (42)	203 (69)	82 (67)		353 (60)
T2a	142 (23)	130 (22)	33 (27)		305 (23)	39.0 (31)	56 (19)	33 (27)		133 (24)
T2b	53 (9)	23 (4)	8 (7)		84 (6)	15 (12)	24 (8)	8 (7)		56 (10)
T2c	39 (6)	13 (2)	0 (0)		52 (4)	18 (14)	10 (3)	0 (0)		32 (6)
<b>Gleason Score</b>				.01 <sup>a,c</sup>					<.001 <sup>b,c</sup>	
≤6	290 (46)	370 (61)	71 (58)		731 (54)	42 (34)	130 (44)	99 (73)		271 (50)
7	280 (45)	207 (34)	48 (39)		535 (40)	61 (49)	122 (42)	32 (24)		215 (39)
≥8	57 (9)	26 (4)	3 (3)		86 (6)	22 (18)	42 (14)	3 (8)		67 (12)
<b>Risk Group</b>				.01 <sup>a,b,c</sup>					<.001 <sup>a,c</sup>	
Low	191 (31)	322 (53)	51 (42)		564 (42)	26 (21)	100 (34)	73 (54)		199 (36)
Intermediate	354 (57)	246 (41)	68 (55)		668 (49)	65 (52)	139 (47)	52 (38)		256 (46)
High	82 (13)	35 (6)	4 (3)		121 (9)	35 (28)	54 (18)	11 (8)		100 (18)

Data are presented as n (%).

Abbreviations: PSA = prostate-specific antigen; USA = United States of America.

<sup>a</sup>Norway versus United States.<sup>b</sup>USA versus Spain.<sup>c</sup>Norway versus Spain.

## Between-Country Differences Before Treatment in PCa

**Data Management and Statistics**

After approval by the local ethical committees, a combined project data file was established, which for each patient contained medical and sociodemographic data (treatment type, risk group, age, education) and EPIC-assessed PROs. The current study investigated only variables before treatment.

Using PASW for PC version 18.0 and separately for the RP and RAD groups, variables were described with means and standard deviations or as proportions. Between-country differences were analyzed using 1-way analysis of variance for continuous variables. Crude associations between pairs of categorical variables were assessed using  $\chi^2$  tests.

Separately for each country, associations between type of treatment (RAD or RP with RP given as a reference) were assessed using univariate and multiple logistic regressions. The strength of associations was expressed according to odds ratios (ORs) and 95% confidence intervals. *P*-values <.01 were considered statistically significant.

**Results**

A total of 1908 patients (1353 planned for RP; 555 planned for RAD) were eligible for the study based on their status before treatment. There were 753 men from Norway (RP: *n* = 627; RAD: *n* = 126), 896 from the United States (RP: *n* = 603; RAD: *n* = 293), and 249 from Spain (RP: *n* = 123; RAD: *n* = 126). The majority of patients from all three countries were caucasian.

**Sociodemographic and Medical Variables**

**Radical Prostatectomy Patients.** In the RP group, significantly more American patients were younger than 65 years old (76%) compared with those from Norway (61%) or Spain (52%) (Table 1). Further, among the US patients we also observed the highest prevalence of men without comorbidities and the highest proportion of patients with at least a high school education. More than half of the American men who received surgery had low-risk tumors compared with 31% and 42% of the Norwegian and Spanish men, respectively. In the Norwegian RP group, significantly more patients had

high-risk disease (13%) compared with the US (6%) and Spanish (3%) groups.

**Radiotherapy Patients.** Within the RAD group, more Norwegian patients were younger than 65 years old compared with the Spanish patients (Table 1). Among the American patients, 72% had completed high school, the comparable proportions being 46% and 12% in the Norwegian and Spanish groups, respectively. More than half of the Spanish patients in the RAD group (54%) had low-risk tumors compared with 21% in the Norwegian and 34% in the US groups. The highest proportion of patients with high-risk tumors was observed in the Norwegian patients (28%).

**Responses to the EPIC-26**

**Urinary Domain.** Independent of country and treatment type, mean scores before treatment were generally high within the urinary domain; the mean urinary incontinence score being >90 for all groups, corresponding to >98% of the patients not using pads (Tables 2 and 3). Thus, summary scores principally reflected the irritative/obstructive urinary dysfunction/bother, with significant between-country differences. Further, only about half of Norwegian and US patients in respectively the RP and RAD group who reported moderate or big dysfunction within the urinary domain also reported problems (Fig. 1). Among the Spanish patients, the proportion of men with obstructive/irritative symptoms and those reporting related problems were more similar.

**Sexual Domain.** In the RP and the RAD groups the lowest mean scores and the highest percentage of patients with moderate/big dysfunction were observed within the sexual domain, with the highest mean scores among the American patients (Tables 2 and 3). Accordingly, the percentages of patients reporting sexual problems were lowest among the US men (RP: 12%; RAD: 18%), and highest among the Spanish men (RP: 28%; RAD: 28%).

In the RAD group approximately half of the patients who reported sexual dysfunction also experienced sexual problems with

**Table 2** Mean EPIC Sum Scores for the 4 Domains for Each Treatment Group in Norway, USA, Spain, and Total Before Treatment

Variable (a)	Radical Prostatectomy					Radiotherapy				
	Norway	USA	Spain	<i>P</i>	Total	Norway	USA	Spain	<i>P</i>	Total
<b>Urinary</b>										
Incontinence score (1, 2, 3, 4a)	94 (12)	94 (13)	94 (15)	.99	94 (13)	93 (11)	92 (14)	96 (11)	.013 <sup>b</sup>	93 (13)
Irritative/obstructive score (4b, c, d, e)	83 (15)	87 (15)	94 (12)	<.001 <sup>b,c,d</sup>	86 (15)	83 (15)	87 (14)	96 (10)	<.001 <sup>b,d</sup>	88 (14)
Overall problem (5)	75 (28)	80 (27)	87 (28)	.013 <sup>b,d</sup>	78 (28)	75 (26)	78 (26)	93 (21)	<.001 <sup>b,d</sup>	81 (26)
<b>Sexual</b>										
Sexual score (8a, b, 9, 10, 11, 12)	67 (25)	78 (23)	62 (25)	<.001 <sup>b,c</sup>	72 (25)	50 (27)	59 (29)	57 (27)	.01 <sup>c</sup>	57 (28)
<b>Bowel</b>										
Bowel score (6a-e, 7)	95 (9)	97 (8)	99 (3)	.002 <sup>b,c,d</sup>	96 (8)	94 (10)	95 (10)	99 (6)	<.001 <sup>b,d</sup>	96 (9)
<b>Hormonal</b>										
Hormonal score (13a-e)	91 (11)	92 (11)	96 (10)	<.001 <sup>b,d</sup>	92 (11)	88 (13)	92 (12)	96 (11)	.001 <sup>b,d</sup>	92 (12)

Data are presented as mean (SD).

Abbreviations: EPIC = Expanded Prostate Cancer Index Composite; USA = United States of America.

<sup>a</sup>EPIC questions used to calculate the mean score.

<sup>b</sup>USA versus Spain.

<sup>c</sup>Norway versus USA.

<sup>d</sup>Norway versus Spain.

**Table 3** Percent of Patients Reporting Specific Levels of Distress or Dysfunction for Each Question in EPIC-26

Variable ( <sup>b</sup> )	Radical Prostatectomy					Radiotherapy				
	Norway (n = 627)	USA (n = 603)	Spain (n = 123)	P	Total (n = 1353)	Norway (n = 126)	USA (n = 293)	Spain (n = 126)	P	Total (n = 555)
<b>Urinary Domain</b>										
Incontinence										
Leaking >1 time per day (1)	3	4	6	.25	4	2	6	1	.04	4
Frequent dribbling (2)	<1	2	3	.06	2	<1	2	<1	.32	2
Any pad use (3)	2	1	<1	.66	1	0	<1	<1	.64	<1
Leaking problem (4a) <sup>c</sup>	2	2	4	.23	2	<1	2	4	.22	2
Irritation or obstruction <sup>c</sup>										
Dysuria (4b)	1	1	2	.28	1	2	1	2	.61	1
Hematuria (4c)	0	<1	<1	.18	<1	0	1	0	.26	<1
Weak stream (4d)	16	12	7	.006 <sup>d</sup>	13	15	13	5	≤.005 <sup>d,e</sup>	12
Frequency (4e)	20	17	11	.01 <sup>d</sup>	18	21	15	2	<.001 <sup>d,e</sup>	14
Overall urinary problem (5) <sup>c</sup>	13	11	13	.59	12	11	11	6	.21	10
<b>Sexual Domain</b>										
Poor erection (8a)	24	14	23	<.001 <sup>f</sup>	20	46	37	27	.003 <sup>d</sup>	37
Difficulty with orgasm (8b)	17	12	15	.071	15	39	32	26	.08	32
Erection not firm for intercourse (9) <sup>g</sup>	27	17	43	<.001 <sup>d,e,f</sup>	24	57	48	52	.263	49
Erection not reliable (10) <sup>h</sup>	27	20	42	≤.004 <sup>d,e,f</sup>	25	52	44	45	.10	46
Poor sexual function (11) <sup>c</sup>	32	13	36	<.001 <sup>e,f</sup>	24	56	34	48	≤.006 <sup>e,f</sup>	43
Overall sexual problem (12) <sup>c</sup>	18	12	28	≤.004 <sup>e,f</sup>	17	27	18	28	.01 <sup>e</sup>	24

Abbreviations: EPIC = Expanded Prostate Cancer Index Composite; USA = United States of America.

<sup>a</sup>The percent of survey respondents reporting the indicated level of dysfunction in the 3 countries in each treatment group and in total in each treatment group.

<sup>b</sup>The number of the EPIC question used.

<sup>c</sup>Moderate or big problem.

<sup>d</sup>Norway versus Spain.

<sup>e</sup>USA versus Spain.

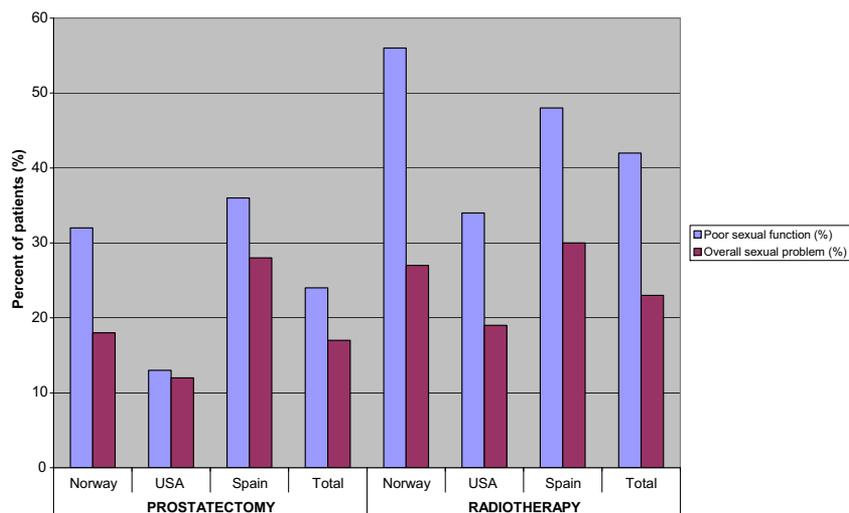
<sup>f</sup>Norway versus USA.

<sup>g</sup>Erection not firm included all answers except "firm enough for intercourse."

<sup>h</sup>Erection approximately half of the time or less was categorized as "erection not reliable."

## Between-Country Differences Before Treatment in PCa

Figure 1 Percent of Patients Reporting Moderate or Big Problem With Frequency And/Or Weak Stream and Overall Urinary Function



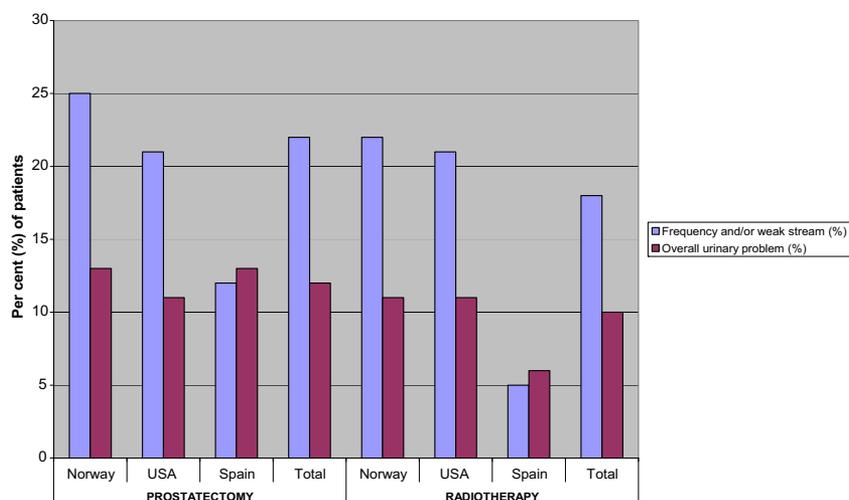
similar patterns across the 3 countries (Fig. 2). In the RP group only for the Spanish and the Norwegian patients, larger differences were observed between sexually dysfunctional men and those reporting related problems. Almost all of the relatively few US patients with sexual dysfunction also reported sexual problems.

*Bowel and Hormonal Domains.* High summary scores in the bowel and hormonal domains were paralleled by low proportions of men reporting problems in these domains (Table 2). Further analyses of these minimally affected domains before treatment were therefore not pursued.

### Multivariate Analyses

In each of the 3 countries, age 65 years or older was significantly associated with being planned for RAD with considerable numerical differences as to the respective ORs (Table 4): Norwegian patients aged 65 years or older were 2.7 times more likely to be planned for RAD than for RP, whereas the comparable likelihood was reflected by an OR of 7 among US men and 4.5 among Spanish patients. Among the American and Norwegian patients, but not among the patients from Spain, comorbidity and presenting with a high-risk tumor were independently associated with RAD. US patients with less than a high school education were twice as likely to receive RAD

Figure 2 Percent of Patients Reporting Poor or Very Poor Ability to Function Sexually and Percentage of Patients Reporting Overall Moderate or Big Problems in the Sexual Domain



**Table 4** Uni- and Multivariate Regression Analysis With RAD the Dependent Variable and RP the Reference

Variable	Norway		USA		Spain	
	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis
<b>Marital Status</b>						
Living together	1.0	—	1.0	—	1.0	—
Not living together	2.9 (1.7-5.2) <sup>a</sup>	2.7 (1.4-5.0) <sup>b</sup>	1.9 (1.3-2.7) <sup>a</sup>	2.4 (1.5-3.7) <sup>a</sup>	1.1 (0.6-2.2) <sup>c</sup>	—
<b>Comorbidity</b>						
No comorbid condition	1.0	—	1.0	—	1.0	—
One or more comorbid condition	2.5 (1.7-3.7) <sup>a</sup>	2.1 (1.4-3.2) <sup>a</sup>	2.6 (1.9-3.7) <sup>a</sup>	1.7 (1.2-2.6) <sup>b</sup>	1.4 (0.9-2.3) <sup>c</sup>	—
<b>Age</b>						
<65 years	1.0	—	1.0	—	1.0	—
≥65 years	3.2 (2.1-4.9) <sup>a</sup>	2.7 (1.7-4.1) <sup>a</sup>	7.7 (5.7-10.6) <sup>a</sup>	7.0 (5.0-10.0) <sup>a</sup>	4.5 (2.8-7.4) <sup>a</sup>	4.8 (2.9-8.2) <sup>a</sup>
<b>Education</b>						
≥High school	1.0	—	1.0	—	1.0	—
<High school	1.3 (0.9-1.8) <sup>c</sup>	—	2.2 (1.5-3.0) <sup>a</sup>	1.9 (1.2-2.9) <sup>b</sup>	0.5 (0.2-1.2) <sup>c</sup>	—
<b>Risk group</b>						
Low	1.0	—	1.0	—	1.0	—
Intermediate	1.3 (0.8-2.2) <sup>c</sup>	1.1 (0.7-2.0) <sup>c</sup>	1.8 (1.3-2.5) <sup>a</sup>	1.5 (1.0-2.1) <sup>b</sup>	0.7 (0.4-1.1) <sup>c</sup>	—
High	3.1 (1.8-5.5) <sup>a</sup>	2.9 (1.6-5.4) <sup>a</sup>	5.0 (3.1-8.0) <sup>a</sup>	3.4 (1.9-6.1) <sup>a</sup>	4.2 (1.4-12.9) <sup>b</sup>	6.9 (2.1-22.2) <sup>a</sup>
<b>EPIC</b>						
Sexual function (question 11)						
Small or less problem	1.0	—	1.0	—	1.0	—
Moderate or big problem	2.6 (1.8-3.9) <sup>a</sup>	1.8 (1.0-2.9) <sup>b</sup>	3.6 (2.5-5.0) <sup>a</sup>	1.9 (1.2-2.9) <sup>b</sup>	2.2 (1.4-3.4) <sup>a</sup>	2.0 (1.2-3.3) <sup>b</sup>
Sexual problem (question 12)						
Small or less problem	1.0	—	1.0	—	1.0	—
Moderate or big problem	1.7 (1.0-2.6) <sup>b</sup>	0.9 (0.5-1.6) <sup>c</sup>	1.6 (1.1-2.4) <sup>b</sup>	1.1 (0.7-1.7) <sup>c</sup>	1.3 (0.8-2.1) <sup>c</sup>	—

Data are presented as OR (95% CI).

Abbreviations: EPIC = Expanded Prostate Cancer Index Composite; RAD = radiotherapy; RP = radical prostatectomy; USA = United States of America.

<sup>a</sup> $P \leq .001$ .

<sup>b</sup> $P > .001 \leq .05$ .

<sup>c</sup> $P > .05$ .

compared with those with higher education levels, with no such association among the Norwegian and Spanish patients. Sexual dysfunction before treatment doubled the likelihood of Norwegian and US patients to receive RAD.

## Discussion

Confirming our hypothesis, significant between-country differences emerged for variables before treatment among Norwegian, American, and Spanish patients planned for either RP or RAD, with the sociodemographic and medical variables differing more in the RP than in the RAD group. American men planned for RP were younger than the European patients. They had comorbidity less often and more patients had a high education level. Fewer US patients than patients from the 2 European countries had an aggressive PCa and fewer of the American men reported sexual dysfunction. Age 65 years or older increased the likelihood to receive RAD for patients from all 3 countries although with considerable between-country variation on the strength of the associations. The proportion of patients with obstructive/irritative urinary dysfunction or impaired sexual function exceeded the percentage of men who experienced problems related to their dysfunction for most patients with between-country differences.

Differences in medical characteristics before treatment (tumor risk group, comorbidity) between patients planned for RP and RAD are well-known from previous studies.<sup>4,24</sup> However, few studies have dealt in depth with between-country variability of the distribution of these parameters before treatment within either the RP or RAD group and of the strength of the association with the final treatment. For each treatment modality (RP or RAD), we observed substantial between-country differences regarding sociodemographic status, disease characteristics, and dysfunctions before treatment within the urinary and sexual domains. Our observations thus add to the results of the study of Namiki et al, which showed that the American patients were younger, healthier, and had less disease burden than men from Japan.<sup>25</sup> We also showed considerable between-country differences of the associations between the elected treatment modality and the medical and sociodemographic variables. Whether these latter observations reflect different views of the responsible doctors or mirror variability of patient preferences cannot be decided based on our data. However, the international literature on typical AEs after treatment has so far considered these before-treatment between-country differences to a limited extent, as a possible explanation for the considerable variations in typical AEs after either RP or RAD reported in the medical literature.

## Between-Country Differences Before Treatment in PCa

Assessment of the patient's typical AEs after curative treatment of PCa usually relies on PROs assessed using questionnaires which often combine dysfunctions and problems as summary scores, which might unjustifiably disregard important differences between dysfunction and bother. In agreement with Gore et al<sup>26</sup> and Reeve et al,<sup>27</sup> our data thus indicate that dysfunction should be separated from problem evaluation, in addition to reporting summary scores: within the urinary domain the proportions of US and Norwegian patients with bother was less than the percentage of men reporting dysfunction. They were apparently less bothered than indicated by their impaired function. We do not have data to explain why many Norwegian and US patients did not regard their impaired urinary function as a problem. Increased voiding frequency and weak stream might, however, be considered as normality among men in that age group. In contrast, the number of men reporting dysfunction and problems was approximately equal among the Spanish patients. They also represented the group with the least urinary dysfunction (urinary frequency or weak stream). We speculated whether elderly Spanish men, more often than the American or Norwegian ones, view impaired voiding as "normal" and therefore report only the most disturbing experiences. Also, in the sexual domain, the proportion of patients with dysfunction exceeded those being bothered, except for the US men who were planned for RP. Many older PCa patients probably accept impaired sexual function as a common consequence of aging and comorbidity. In contrast, among the younger and healthier US patients in the RP group, impaired sexual function was more often reported as a bothersome loss.

In the multivariate analyses, and similar for the US and Norwegian patients, we observed that erectile dysfunction before treatment doubled the likelihood to receive RAD. We have no good explanation for this finding and tend to view this observation as a "finding by chance."

Our findings of the between-country differences of the mean scores of self-reported sexual and erectile function and overall sexual problems within the RP and RAD groups are new. We speculate whether such between-country differences, at least in part can explain the variability of erectile dysfunction after treatment as reported in review articles including studies from multiple countries.<sup>9</sup> Several previous analyses have documented that good erectile and urinary function before treatment predicts a satisfactory outcome within these domains after treatment, together with young age.<sup>11,12,28</sup> Planned analyses of our patients' PROs after treatment will address these issues.

### Strengths and Limitations

Selection bias can not be overlooked in our study: RP was planned in more than half of our patients, in particular, in those from the American and Norwegian cohorts. This observation requires an explanation: for patients with T1 or T2 tumors, the most common treatment in America and in Norway is RP, especially in the younger ones.<sup>29,30</sup> However, this tendency was not observed in the Spanish cohort. Most probably the country-related differences in our study as to RP versus RAD mirror different treatment strategies and different patient views. Second, well-educated, sexually active American men might have selected recognized institutions for their treatment, whereas the Spanish and Norwegian men probably had this opportunity to a lesser degree and were probably more

likely to represent the average patient with localized PCa diagnosed in the respective country. Third, our study covers the past decade, when also other treatment modalities were available such as low-dose RAD or active surveillance. For our patients, we lack detailed information on all selection criteria for the choice of RP or RAD. We also do not know the degree to which the final treatment election was based on the patient's or doctor's preferences, or whether the patients had been informed about the different treatment options and their AEs. In this mainly descriptive study we have therefore refrained from discussing the analyzed variables as selection criteria. Sufficient information on the use of erectile aids before treatment, important for evaluation of erectile function, was not available. Finally, the limited number of non-Caucasian patients prevented analysis of our data stratified for race.

The main strengths of our study are the large sample size and the use of the same questions to evaluate function and problems within the domains expected to be affected by curative treatment of PCa. The fact all patients were hormone-naïve before questionnaire completion is regarded as an advantage.

### Conclusion

In PCa patients from Norway, the United States, or Spain who were planned to receive RP or RAD, considerable between-country differences were confirmed before treatment regarding age and risk group.

### Clinical Practice Points

- Our results as to considerable between-group differences of dysfunction and bother within the sexual and urinary domain are new.
- Because factors before treatment might be related to outcomes after treatment, they should not be overlooked regarding published differences of outcomes across countries.
- The finding of considerable discrepancies between dysfunction and problem experience within the urinary and sexual domain is a new observation and should be taken into account in counseling a patient with PCa before final choice of treatment modality.

### Acknowledgments

PROSTQA Template for Group Credit PROSTQA Consortium study group (Study Investigators, DCC and Coordinators): The PROSTQA Consortium includes contributions in cohort design, patient accrual and follow-up from the following investigators: Meredith Regan (Dana Farber Cancer Institute, Boston, MA); Larry Hembroff (Michigan State University, East Lansing, MI); John T. Wei, Dan Hamstra, Rodney Dunn, Laurel Northouse and David Wood (University of Michigan, Ann Arbor, MI); Eric A Klein and Jay Ciezki (Cleveland Clinic, Cleveland, OH); Jeff Michalski and Gerald Andriole (Washington University, St. Louis, MO); Mark Litwin and Chris Saigal (University of California—Los Angeles Medical Center, Los Angeles, CA); Thomas Greenfield, PhD (Berkeley, CA), Louis Pisters and Deborah Kuban (MD Anderson Cancer Center, Houston, TX); Howard Sandler (Cedars Sinai Medical Center, Los Angeles, CA); Jim Hu and Adam Kibel (Brigham and Women's Hospital, Boston, MA); Douglas Dahl and Anthony Zietman (Massachusetts General Hospital, Boston, MA); Peter Chang Andrew Wagner, and Irving Kaplan (Beth Israel

Deaconess Medical Center, Boston, MA) and Martin G. Sanda (Emory, Atlanta, GA). We acknowledge PROSTQA Data Coordinating Center Project Management by Jill Hardy, MS (Michigan State University, East Lansing, MI), Erin Najuch and Jonathan Chipman (Dana Farber Cancer Institute, Boston, MA) and Catrina Crociani, MPH (Beth Israel Deaconess Medical Center, Boston, MA), grant administration by Beth Doiron, BA (Beth Israel Deaconess Medical Center, Boston, MA), and technical support from coordinators at each clinical site. The Multicentric Spanish Group of Clinically Localized Prostate Cancer. The project is funded by the PROSTQA grants (NIH R01 CA95662; NIH 1RC1CA146596) and grants from Instituto de Salud Carlos III FEDER, (PI13/00412).

## Disclosure

The authors have stated that they have no conflicts of interest.

## References

- Kibel AS, Ciezki JP, Klein EA, et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol* 2012; 187:1259-65.
- Mendenhall WM, Nichols RC, Henderson R, Mendenhall NP. Is radical prostatectomy the "gold standard" for localized prostate cancer? *Am J Clin Oncol* 2010; 33:511-5.
- Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med* 2008; 148:435-48.
- Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013; 368:436-45.
- Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 2004; 96:1358-67.
- Namiki S, Kwan L, Kagawa-Singer M, Terai A, Arai Y, Litwin MS. Urinary quality of life after prostatectomy or radiation for localized prostate cancer: a prospective longitudinal cross-cultural study between Japanese and U.S. men. *Urology* 2008; 71:1103-8.
- Hugosson J, Stranne J, Carlsson SV. Radical retropubic prostatectomy: a review of outcomes and side-effects. *Acta Oncol* 2011; 50(suppl 1):92-7.
- Alivizatos G, Skolarikos A. Incontinence and erectile dysfunction following radical prostatectomy: a review. *Scient World J* 2005; 5:747-58.
- Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. *J Sex Med* 2009; 6:2538-46.
- Burnett AL, Aus G, Canby-Hagino ED, et al. Erectile function outcome reporting after clinically localized prostate cancer treatment. *J Urol* 2007; 178:597-601.
- Pinkawa M, Gagel B, Piroth MD, et al. Erectile dysfunction after external beam radiotherapy for prostate cancer. *Eur Urol* 2009; 55:227-34.
- Wille S, Heidenreich A, Hofmann R, Engelmann U. Preoperative erectile function is one predictor for post prostatectomy incontinence. *Neurourol Urodyn* 2007; 26:140-3.
- Namiki S, Kwan L, Kagawa-Singer M, et al. Sexual function reported by Japanese and American men. *J Urol* 2008; 179:245-9.
- 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 Rad Oncol Biol Phys* 2008; 72:421-32.
- Pardo Y, Guedea F, Aguiló F, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. *J Clin Oncol* 2010; 28:4687-96.
- Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *New Engl J Med* 2008; 358:1250-61.
- Steinsvik EA, Axcrona K, Angelsen A, et al. Does a surgeon's annual radical prostatectomy volume predict the risk of positive surgical margins and urinary incontinence at one-year follow-up? Findings from a prospective national study. *Scand J Urol Nephrol* 2013; 47:92-100.
- Steinsvik EA, Axcrona K, Dahl AA, Eri LM, Stensvold A, Fossa SD. Can sexual bother after radical prostatectomy be predicted preoperatively? Findings from a prospective national study of the relation between sexual function, activity and bother. *Br J Int* 2012; 109:1366-74.
- Lilleby W, Tafjord G, Raabe NK. Implementation of high-dose-rate brachytherapy and androgen deprivation in patients with prostate cancer. *Int J Rad Oncol Biol Phys* 2012; 83:933-9.
- Guidelines on Prostate Cancer. 2012. Available at: [www.uroweb.org](http://www.uroweb.org)
- Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. 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.
- Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the Expanded Prostate Cancer Index Composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010; 76:1245-50.
- Sanda MG, Wei JT, Litwin MS. Scoring instructions for the Expanded Prostate Cancer Index Composite Short Form (EPIC-26). 2007. Available at: <http://www.med.umich.edu/urology/research/EPIC/EPIC-Scoring-2.2002.pdf>
- Huang GJ, Sadetsky N, Penson DF. Health-related quality of life for men treated for localized prostate cancer with long-term follow-up. *J Urol* 2010; 183:2206-12.
- Namiki S, Kwan L, Kagawa-Singer M, et al. Sexual function following radical prostatectomy: a prospective longitudinal study of cultural differences between Japanese and American men. *Prostate Cancer Prostatic Dis* 2008; 11:298-302.
- Gore JL, Gollapudi K, Bergman J, Kwan L, Krupski TL, Litwin MS. Correlates of bother following treatment for clinically localized prostate cancer. *J Urol* 2010; 184:1309-14.
- Reeve BB, Potosky AL, Willis GB. Should function and bother be measured and reported separately for prostate cancer quality-of-life domains? *Urology* 2006; 68:599-603.
- Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. *JAMA* 2011; 306:1205-14.
- Hamilton AS, Albertsen PC, Johnson TK, et al. Trends in the treatment of localized prostate cancer using supplemented cancer registry data. *BJU Int* 2011; 107:576-84.
- Fossa SD, Nilssen Y, Kvale R, Hernes E, Axcrona K, Moller B. Treatment and 5-year survival in patients with nonmetastatic prostate cancer: the norwegian experience. *Urology* 2014; 83:146-53.