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,[1] Martin G. Sanda,[2] Montse Ferrer,[3] Jon Håvard Loge,[1,4] Alv A. Dahl,[1,4] Eivind A.S. Steinsvik,[5] Ferran Guedea,[6] Milada Cvancarova,[1] Sophie D. Fosså[1,4]

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 prostatecomy (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 sociodemographic 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 bother 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.

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[1]Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway
[2]Department of Urology, Emory University Hospital, Atlanta, GA
[3]Health Services Research Group, IMIM (Hospital del Mar Research Institute), Barcelona, Spain
[4]Faculty of Medicine, University of Oslo, Oslo, Norway
[5]Department of ENT, Division of Surgery, Akershus University Hospital, Lorenskog, Norway
[6]Department of Radiation Oncology, Catalan Institute of Oncology, L'Hospitalet de Llobregat, Barcelona, Spain

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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

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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.[1-3] However, the patterns of "typical adverse effects (AEs)" (dysfunction within the urinary, sexual, bowel, and hormonal domains and related problems) differ substantially.[4,5] 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.[6-10] 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.[11,12] 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.[13]

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 Assesment) 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.[14-18] 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 prostatecomy 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.[19]

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.[20]

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) ulcus 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")[21] and hormone treatment-related AEs.[21,22] The original questionnaire includes 50 items (EPIC-50) but was later abbreviated to 26 items (EPIC-26).[22] 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.[23] 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,[16] 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.