Measuring and Predicting Prostate Cancer Related Quality of Life Changes Using EPIC for Clinical Practice

Jonathan J. Chipman, Martin G. Sanda, Rodney L. Dunn, John T. Wei, Mark S. Litwin, Catrina M. Crociani, Meredith M. Regan, Peter Chang* and the PROST-QA Consortium

From the Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute (JJC, MMR), Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center (CMC, PC) and Harvard Medical School (MMR, PC), Boston, Massachusetts, Department of Urology, Emory University (MGS), Atlanta, Georgia, Department of Urology, University of Michigan School of Medicine (RLD, JTW), Ann Arbor, Michigan, and David Geffen School of Medicine and Fielding School of Public Health, University of California-Los Angeles (MSL), Los Angeles, California

Abbreviations and Acronyms

HRQOL = health related quality of life

MID = minimally important difference

PCa = prostate cancer

PRO = patient reported outcome

PSA = prostate specific antigen

Accepted for publication September 18, 2013.

Study received institutional review board approval.

Supported by National Institutes of Health Grants R01 CA95662 and RC1 CA146596, and a grant from the UrologyCare Foundation Research Scholars Program and Dornier Medtech entitled "Measuring Prostate Cancer Patient Reported Outcomes at the Point of Care."

* Correspondence: Division of Urology, Harvard Medical School, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Rabb 440, Boston, Massachusetts 02215 (telephone: 617-667-3739; FAX: 617-667-2883; e-mail: pchang@bidmc.harvard.edu).

Purpose: We expanded the clinical usefulness of EPIC-CP (Expanded Prostate Cancer Index Composite for Clinical Practice) by evaluating its responsiveness to health related quality of life changes, defining the minimally important differences for an individual patient change in each domain and applying it to a sexual outcome prediction model.

Materials and Methods: In 1,201 subjects from a previously described multicenter longitudinal cohort we modeled the EPIC-CP domain scores of each treatment group before treatment, and at short-term and long-term followup. We considered a posttreatment domain score change from pretreatment of 0.5 SD or greater clinically significant and $p \leq 0.01$ statistically significant. We determined the domain minimally important differences using the pooled 0.5 SD of the 2, 6, 12 and 24-month posttreatment changes from pretreatment values. We then recalibrated an EPIC-CP based nomogram model predicting 2-year post-prostatectomy functional erection from that developed using EPIC-26.

Results: For each health related quality of life domain EPIC-CP was sensitive to similar posttreatment health related quality of life changes with time, as was observed using EPIC-26. The EPIC-CP minimally important differences in changes in the urinary incontinence, urinary irritation/obstruction, bowel, sexual and vitality/hormonal domains were 1.0, 1.3, 1.2, 1.6 and 1.0, respectively. The EPIC-CP based sexual prediction model performed well (AUC 0.76). It showed robust agreement with its EPIC-26 based counterpart with 10% or less predicted probability differences between models in 95% of individuals and a mean $\pm$ SD difference of 0.0 ± 0.05 across all individuals.

Conclusions: EPIC-CP is responsive to health related quality of life changes during convalescence and it can be used to predict 2-year post-prostatectomy sexual outcomes. It can facilitate shared medical decision making and patient centered care.

Key Words: prostate, prostatic neoplasms, quality of life, questionnaires, outcome assessment (health care)

Evaluation of HRQOL in patients with PCa without a PRO questionnaire underestimates the severity of side effects.[1] Practitioners should be capable of counseling patients about these effects before treatment as well

0022-5347/14/1913-0638/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.09.040
Vol. 191, 638-645, March 2014
Printed in U.S.A.

as accurately recognizing and managing any posttherapy HRQOL deficits.

Several existing PCa PRO instruments, such as UCLA-PCI[2] and EPIC,[3,4] can accurately evaluate PCa related HRQOL changes with time.[5] Researchers have also developed multivariable models that can predict posttreatment outcome based on pretreatment HRQOL.[6] However, these instruments are used mostly for research since they are too lengthy and time-consuming to be used in clinical practice. This limits the ability of PCa practitioners to accurately assess HRQOL and optimally individualize treatment related decisions.

To bridge the research and clinical realms we previously developed EPIC-CP, a 16-item PRO questionnaire designed specifically for clinical use at the point of care. We reported that it has good internal consistency, reliability and discriminative validity, correlates highly with previous EPIC versions[3,4] and is convenient to use in the flow of routine practice.[7] However, we had not yet studied the responsiveness of EPIC-CP to treatment related HRQOL changes with time.

Most PCa HRQOL PRO questionnaires, including EPIC-CP, group questions together into health domains (eg bowel and sexual) and represent outcomes using numerical domain scores. This is useful to examine trends or average changes in HRQOL with time but it can present challenges in clinical interpretation. For example, if the EPIC-CP sexual score of a patient improves by 2 points between 6 and 12 months after brachytherapy, does this represent a statistical phenomenon or a clinically relevant change for the patient?

In this study we had 3 objectives. 1) We evaluated the responsiveness of EPIC-CP to posttreatment HRQOL changes with time. 2) We increased the clinical interpretability of EPIC-CP by defining clinically meaningful score changes for each domain. 3) We applied EPIC-CP to a clinically useful tool that uses the pretreatment EPIC-26 sexual score to predict posttreatment outcome and compared the performance of the new EPIC-CP based tool with its EPIC-26 based counterpart.

METHODS

Study Population

We evaluated subjects from the previously described PROST-QA (Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment) cohort.[8] This multicenter, institutional review board approved, prospective study included 1,201 men with early stage PCa who elected radical prostatectomy with or without nerve sparing, external beam radiotherapy with or without neoadjuvant hormonal therapy, or brachytherapy with or without external beam radiotherapy and/or neoadjuvant hormonal therapy from 2003 to 2006 at a total of 9 university affiliated hospitals. The EPIC-26 item responses of these 1,201 men were used to calculate their respective EPIC-CP scores.

EPIC-CP Analysis and Statistical Considerations

Responsiveness to average posttreatment HRQOL changes with time. To model the EPIC-CP domain scores of each of the 6 treatment groups before treatment, and at short-term and long-term followup we used generalized estimating equations with a compound symmetry working covariance structure. We defined short-term as 2 or 6 months after treatment based on which time point showed a greater EPIC-26 domain difference from pretreatment baseline.[8] Long-term was defined as 24 months after treatment. The EPIC-CP domain scores of each treatment group that differed from pretreatment values at $p \leq 0.01$ using the Bonferroni adjustment for multiple comparisons were considered statistically significantly different. Analogous to the original PROST-QA study,[8] domain scores that differed by at least 0.5 SD of the pretreatment score were considered clinically significant.

Clinically meaningful HRQOL changes. A clinically meaningful HRQOL change, also known as the MID, is defined as the domain specific summary score change threshold (usually a narrow range) at and above which an individual perceives a clinically relevant HRQOL change. We used the generally accepted Cohen effect size standard of 0.5 SD to represent a moderately sized, clinically relevant intra-individual HRQOL change.[9] To calculate the MID a distribution based method was applied that emphasized intra-individual changes in scores with time. For each domain and treatment group we determined the 0.5 SD of pretreatment scores, calculated the 0.5 SDs of intra-individual score changes from before treatment, and 2, 6, 12 and 24 months after treatment, and determined the pooled 0.5 SD of the change from pretreatment score. This value was considered the MID for each treatment group. For each domain we used the pooled 0.5 SD of the change from pretreatment score across time points and across treatments to calculate the overall MID independently of treatment group.

Multivariable predictive nomogram. We previously developed and externally validated an EPIC-26 based multivariable nomogram that uses the pretreatment sexual domain score to predict the probability of functional erection, defined as achieving erection firm enough for intercourse, 2 years after treatment.[5] To adapt this tool for point of care clinical use in men planning radical prostatectomy we used the same covariates of age, planned nerve sparing approach and PSA 10 ng/ml or less to recalibrate the multivariable logistic regression prediction model using the pretreatment EPIC-CP sexual score in the 493 patients treated with prostatectomy (of the 524 previously analyzed[5]) who answered all EPIC-CP sexual domain questions. We examined Pearson residuals to ensure that the recalibrated model was well fit. We then determined the predicted probabilities in each individual