Quality of Life for Men Receiving a Second Treatment for Prostate Cancer

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Purpose: We assessed the impact of second treatment on health related quality of life for men with prostate cancer. This issue is important because second treatment resulting from prostate specific antigen recurrence has the potential to further negatively impact health related quality of life and affect the overall value of treatment. We compared differences in health related quality of life before and after second treatment for men who had asymptomatic prostate specific antigen recurrence with those who did not have biochemical failure.

Materials and Methods: Men in this analysis (897) had localized disease, initially underwent radical prostatectomy monotherapy, and completed at least 1 health related quality of life questionnaire before and after radical prostatectomy. In this cohort 175 men underwent second treatment (nonadjuvant). The Medical Outcomes Survey Short Form-36 and UCLA Prostate Cancer Index were used to measure health related quality of life. Associations between patient groups and time on health related quality of life were analyzed using repeated measures.

Results: Men who received a second treatment presented with more severe disease before radical prostatectomy and had worse general health related quality of life. Although health related quality of life differed significantly with time for the 2 groups, most domains for the second treatment group improved or remained stable until 15 months before second treatment, at which point they declined. Scores in the sexual functioning and role-physical domains showed clinically and statistically significant patterns of decreasing with time.

Conclusions: Health related quality of life is affected following second treatment but starts to decline approximately 1 year before second treatment. Not all aspects of health related quality of life decreased at the same rate, so patients should be counseled that certain domains may be affected more by additional treatment.

Key Words: quality of life, prostatic neoplasms, outcome assessment

Prostate specific antigen screening has increased the number of men being diagnosed with clinically localized prostate cancer, and most are treated.[1] Radiation therapy and radical prostatectomy have been the primary treatment choices for such men, and their use has increased.[2] Because of the changes in HRQOL related to PCa treatment, patients and clinicians often need to make a complex decision about treatment that takes into account quantity and quality of life.

Health related quality of life is an important issue for men undergoing definitive treatment because of treatment related side effects and the protracted natural history of the disease.[3] Approximately a third of men treated with RP will have biochemical recurrence preceding symptomatic recurrence and death by many years in most cases.[4] Management of biochemical recurrence has been controversial due to concerns regarding possible additional decreases in HRQOL.

While several recent publications have reported HRQOL in men treated for localized PCa,[5–8] less is known

Submitted for publication January 11, 2006.

CaPSURE is supported by TAP Pharmaceutical Products Inc. (Lake Forest, Illinois).

Supported by National Institutes of Health/National Cancer Institute University of California-San Francisco SPORE Specialized Program of Research Excellence P50 C89520.

Supported with resources and the use of facilities at the Houston Center for Quality of Care and Utilization Studies, Houston Veterans Affairs Medical Center.

* Nothing to disclose.

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‡ Financial interest and/or other relationship with TAP Pharmaceuticals, NCI, DOD and ACS.

§ Financial interest and/or other relationship with TAP.

‖ Financial interest and/or other relationship with Ovation Research Group and Sanofi-Aventis.

¶ Financial interest and/or other relationship with NIH, DOD, TAP, Informedical, ICPME and AstraZeneca.

Editor's Note: **This article is the fifth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 410 and 411.**

Vol. 177, 273-279, January 2007
Printed in U.S.A.
DOI:10.1016/j.juro.2006.08.061

about how HRQOL changes over time for men with recurrent disease.[9] Two small cross-sectional studies have examined HRQOL in men with recurrent PCa initially treated with surgery. Tefilli et al compared HRQOL in men with recurrent disease treated with surgery or radiation as salvage therapy.[10] Few differences were found between groups. Patients treated with salvage radiation had significantly better physical well-being and better urinary functioning than men treated with salvage surgery. Pietrow et al studied HRQOL in men with and without PSA recurrence after RP, and found significant differences in 2 domains of the Medical Outcomes Survey SF-36 (physical functioning and role-emotional) and 1 domain of the UCLA PCI (bowel bother).[11]

In this report we build on these earlier studies of men with recurrent PCa by examining HRQOL longitudinally for patients undergoing RP without recurrent disease compared with patients undergoing RP who received a second treatment for recurrent disease. This longitudinal approach allowed us to examine HRQOL before initial treatment for PCa as well as after recurrence to understand whether men who will eventually have recurrence and receive a second treatment present with poorer baseline HRQOL. We also determined whether patterns of HRQOL over time would differ for men receiving a second treatment after recurrence vs men without recurrence.

MATERIALS AND METHODS

Study Population

CaPSURE is a longitudinal, observational PCa disease registry with 31 sites nationwide currently enrolling participants. Sites are primarily community urology practices with only about 8% of study participants from academic or Veterans Administration practices. Patient care varies according to the physician usual practices, and semiannual questionnaires collect information about HRQOL until time of death or study withdrawal. During the first 4 years of the study data were collected on patients with incident and prevalent PCa. Since 1999 only incident cases have been enrolled in study. Additional details about project methodology have been previously reported.[12]

We examined outcomes for men who received RP as initial therapy, had localized disease, and completed at least a HRQOL questionnaire before and after RP. A total of 4,128 patients were identified as having RP as initial treatment. A subset of this group underwent a second treatment (nonadjuvant), defined as treatment more than 6 months after RP. Second treatment in this cohort was either radiation or hormonal therapy. Men who had second treatment completed, at a minimum, 1 HRQOL questionnaire after RP, 1 before second treatment and 1 after second treatment.

Outcomes Measured

The SF-36 version 1.0 health survey was used to measure general HRQOL.[13] This survey consists of 8 individual domains, and 2 summary scores measuring physical and mental HRQOL. The 8 individual domains include physical functioning, role-physical, role-emotional, vitality, mental health, social functioning, bodily pain and general health. Each domain is scored from 0 to 100, with higher scores representing better outcomes. The mental component and physical component summaries are scored so that a score of 50 represents a standardized mean.

The UCLA PCI quantifies PCa specific HRQOL in 6 separate domains of urinary function, urinary bother, bowel function, bowel bother, sexual function and sexual bother.[14] The scales are scored from 0 to 100, with higher scores denoting better function and less bother. A clinically meaningful change is expressed with differences of 5 to 10 points on the SF-36 and PCI scales.[15,16]

HRQOL outcomes were measured using a questionnaire mailed to participants biannually in January and July, with most questionnaires returned within 3 months of initial mailing. In this analysis we used this 3-month midpoint between mailings as the interval for our comparisons. Since men in the RP only group had no second treatment, we established a comparable point in their followup history by calculating the median time between RP and second treatment for men in the second treatment group (37.3 months). With the data available we compared HRQOL outcomes longitudinally from 27 months before second treatment up to 39 months after second treatment.

Statistical Methods

Clinical and sociodemographic characteristics were analyzed using the chi-square test for discrete variables and ANOVA for continuous variables. We examined HRQOL at baseline with a model adjusting for baseline clinical and sociodemographic characteristics including biopsy Gleason score, clinical T stage, PSA at diagnosis, ethnicity, age at diagnosis and education. Longitudinal changes in HRQOL were evaluated using a repeated measures approach for each HRQOL domain. This analytic method accounts for the likelihood an individual's score on a given outcome measure at 1 point is likely to be strongly related to the score on the same outcome at the next point. In addition, it handles missing values and participant attrition in an optimal way by taking into account the time patterns of available data. The repeated measures model was adjusted for the same characteristics as the baseline comparison, and included main effects for group (either RP only or RP plus second treatment) and time. To determine whether the patterns of HRQOL differed between the 2 groups over time, the model also included an interaction term for group by time period. No formal adjustment was made for multiple comparisons and $p < 0.05$ was used as the estimate for reporting statistical significance. All analyses were performed using SAS® version 9.1.

RESULTS

After eliminating participants without the HRQOL questionnaires from the 4,128 men undergoing RP as initial therapy, there were 722 men in the RP only group, 175 men in the RP plus second treatment group and 35 men with evidence of biochemical recurrence who lacked second treatment information. Given the small number in this last group, we excluded them from analysis, leaving a final sample of 897 men. These 35 men did not differ from the 897 included in the analysis on any sociodemographic characteristics or most baseline clinical characteristics. The excluded men did have significantly higher Gleason

scores and less advanced T stage at baseline than men included in the analysis.

Baseline sociodemographic and clinical characteristics of this cohort of patients are presented by group (RP only vs RP plus second treatment) in table 1. There were no differences between groups in age, ethnicity, educational level or income. Men who received a second treatment for PCa presented with significantly more severe disease before RP as demonstrated by higher PSA levels, higher Gleason scores and more advanced staging. They were also significantly less likely to have nerve sparing surgery and significantly more likely to have positive surgical margins.

We examined HRQOL before RP (table 2, unadjusted p value, column 4), and found significant differences between groups in general health, health transitions, mental health, physical functioning, role-emotional, vitality, and mental and physical component scores. There were fewer differences in disease specific HRQOL, with only bowel bother being statistically different between groups. Across all domains in which significant differences were found, men in the RP plus second treatment group reported worse HRQOL than men in the RP only group at baseline. These differences were generally maintained once we adjusted for baseline clinical and sociodemographic characteristics (table 2, adjusted p value, column 5). We also found differences in sexual functioning and sexual bother.

We then examined patterns of HRQOL over time for the 2 groups, while adjusting for the same baseline clinical and sociodemographic characteristics as in the baseline analysis (table 2). To understand the impact of group membership on HRQOL over time, we included a time-by-group interaction term in the repeated measure models (table 2). Two HRQOL domains showed statistically and clinically significant differences over time. For the role-physical domain there was no difference between groups at baseline (table 2), but starting at 27 months before second treatment the groups were different (fig. 1). Men in the RP plus second treatment group reported an improvement in the role-physical domain but condition began to decline again as they neared the second treatment. These differences continued throughout the 39 months after second treatment.

We observed a somewhat similar pattern for sexual functioning. Men in the 2 groups did not differ at baseline (table 2) and had similar scores up to 15 months before second treatment. After this time the groups began to diverge (fig. 2) and this difference remained fairly constant throughout the rest of the observation period. Other HRQOL domains showed a similar pattern of decline approximately 12 to 18 months before second treatment, with physical HRQOL domains tending to decrease before mental-emotional domains. We observed significant differences over time in these other domains, as evidenced by the significant interaction term in table 2. However, while these differences may have been statistically significant, the absolute differences in most of these domains were small and, thus, unlikely to be of clinical significance.[15,16] For men who received a second treatment, we fit a set of models for each domain that included a 3-level variable for type of second treatment (radiotherapy or hormonal therapy). There were no differences in any of the HRQOL domains by type of second treatment (data not shown).

DISCUSSION

We examined baseline characteristics and HRQOL over time for 2 groups of men treated with radical prostatectomy: those who received an RP as monotherapy and those with an RP as a first treatment followed by biochemical recurrence and a second treatment. While the 2 groups had no differences in sociodemographic characteristics, men who went on to require a second treatment for PCa presented with significantly more severe disease at baseline. Men who underwent a second treatment also reported significantly worse HRQOL at baseline, although absolute differences between groups at baseline were small enough to be of limited clinical significance.

The number of men with biochemical recurrence who lacked second treatment data was too small (35) for inclusion in our analyses. Since the excluded men had significantly more advanced disease it is likely these men would have had a second treatment, and their inclusion would likely have increased the differences detected between the RP only and RP plus second treatment groups. Studies enrolling more men with recurrence who do not seek second treatment would permit a finer-grained understanding of the impact on HRQOL of biochemical recurrence vs biochemical recurrence plus second treatment. However, given the concern many patients with PCa express on finding their PSA results increasing after completing primary treatment, it might be difficult to find enough men with biochemical recurrence willing to forego second treatment.

Health related quality of life is affected before and after second treatment for men with PSA recurrence. These men usually have a decrease in HRQOL that starts 15 months before the second treatment. All HRQOL domains showed statistically significant differences over time, with 2 of those

TABLE 1. *Baseline sociodemographic and clinical characteristics*

	No. RP Only (%)	No. RP + Treatment 2 (%)	p Value
Age at diagnosis:			
Younger than 60	263 (36.6)	54 (30.7)	0.10
60–70	398 (55.4)	100 (56.8)	
Older than 70	58 (8.1)	22 (12.5)	
Race/ethnicity:			
White	627 (87.2)	159 (90.3)	0.25
Other	92 (12.8)	17 (9.7)	
Education level:			
Less than high school	78 (11.2)	25 (14.7)	0.29
High school	175 (25.1)	49 (28.8)	
Some college	136 (19.5)	33 (19.4)	
BA + beyond	308 (44.2)	63 (37.1)	
Yearly household income:			
Less than $30,000	154 (24.9)	42 (28.5)	0.08
$30,000–$50,000	176 (28.5)	53 (36.1)	
$50,000–$75,000	134 (21.7)	21 (14.2)	
Greater than $75,000	153 (24.8)	31 (21.1)	
PSA at diagnosis (ng/ml):			
Less than 4	128 (21.0)	31 (25.4)	<0.0001
4–10	448 (73.3)	64 (52.5)	
10–20	35 (5.7)	27 (22.1)	
T stage:			
T1	200 (28.2)	34 (20.4)	0.0052
T2	494 (69.7)	123 (73.7)	
T3	15 (2.1)	10 (6.0)	
Gleason score:			
2–6	544 (78.6)	92 (59.0)	<0.0001
7	121 (17.5)	38 (24.4)	
8–10	27 (3.9)	26 (16.7)	
Nerve sparing surgery	459 (63.8)	87 (49.2)	<0.0001
Pos margins	149 (27.6)	64 (53.8)	<0.001

TABLE 2. *HRQOL comparisons*

	Baseline Analysis				Longitudinal Analysis
	No. RP Only (%)	No. RP + Treatment 2 (%)	Unadjusted p Value	Adjusted p Value*	Time × Group Interaction*
SF-36 subscales:					
Bodily pain	82.2 (21.3)	79.5 (22.9)	Not significant	<0.001	<0.0001
General health	76.3 (18.5)	71.1 (18.7)	<0.01	<0.001	<0.0001
Health transitions	55.9 (24.2)	50.4 (22.9)	<0.01	<0.01	<0.05
Mental health	80.5 (15.6)	77.2 (17.9)	<0.05	<0.0001	<0.05
Physical functioning	84.6 (20.9)	80.2 (23.0)	<0.05	<0.0001	<0.0001
Role-emotional	82.5 (33.3)	76.6 (36.4)	<0.05	<0.01	<0.001
Role-physical	69.3 (41.7)	67.6 (42.7)	Not significant	<0.05	<0.0001
Social functioning	84.2 (23.2)	81.9 (27.5)	Not significant	<0.001	<0.0001
Vitality	65.9 (19.1)	62.3 (21.3)	<0.05	<0.001	<0.001
Mental component score	52.7 (8.7)	50.7 (10.8)	<0.05	<0.001	<0.001
Physical component score	49.6 (9.1)	48.0 (9.5)	<0.05	<0.001	<0.0001
UCLA Prostate Cancer Index subscales:					
Urinary function	71.6 (26.7)	69.9 (28.2)	Not significant	Not significant	<0.0001
Urinary bother	72.3 (30.2)	73.4 (30.1)	Not significant	Not significant	<0.001
Bowel function	85.6 (17.2)	84.1 (18.4)	Not significant	Not significant	<0.0001
Bowel bother	87.2 (23.0)	82.9 (27.7)	<0.05	Not significant	<0.001
Sexual function	28.1 (27.2)	25.6 (27.8)	Not significant	<0.0001	<0.0001
Sexual bother	42.0 (39.4)	40.8 (38.7)	Not significant	<0.001	<0.01

* Adjusted for biopsy Gleason score, clinical T stage, PSA at diagnosis, ethnicity, age at diagnosis and educational level.

(role-physical and sexual functioning) showing large enough differences over time to be clinically relevant to patients. Men in the second treatment group presented with more severe disease, were less likely to have nerve sparing surgery and were more likely to have positive margins. These factors may account in part for some of the group differences in HRQOL, particularly in sexual functioning.

While the research literature on HRQOL for men with recurrent PCa is limited, the consensus of Litwin's recent review of 12 published studies is that combination therapy for PCa has the potential for substantial impact on HRQOL.[9] Most of these studies have been cross-sectional in nature, limiting the ability to control for baseline characteristics or to see change over time. The current results are the first opportunity to our knowledge to examine differences in patterns of HRQOL longitudinally.

The differences we found in HRQOL are consistent with previous research that looked at HRQOL after androgen deprivation,[11,17,18] radiation,[10] or androgen deprivation and radiation[19] in men who previously were treated with RP. Hu et al found similar decreases in disease specific HRQOL for men undergoing salvage radiation after RP.[20] The larger differences we observed in HRQOL domains could be due to additional information gained by assessing HRQOL before second treatment and longer periods of followup after second treatment than other studies.

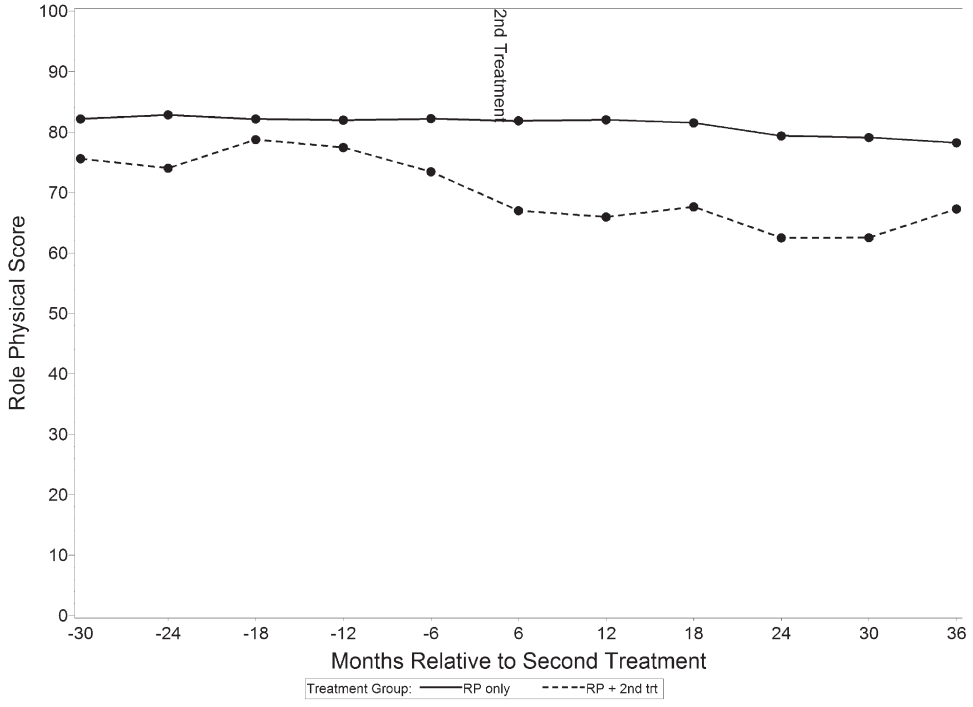

FIG. 1. Patterns of role-physical over time by treatment group

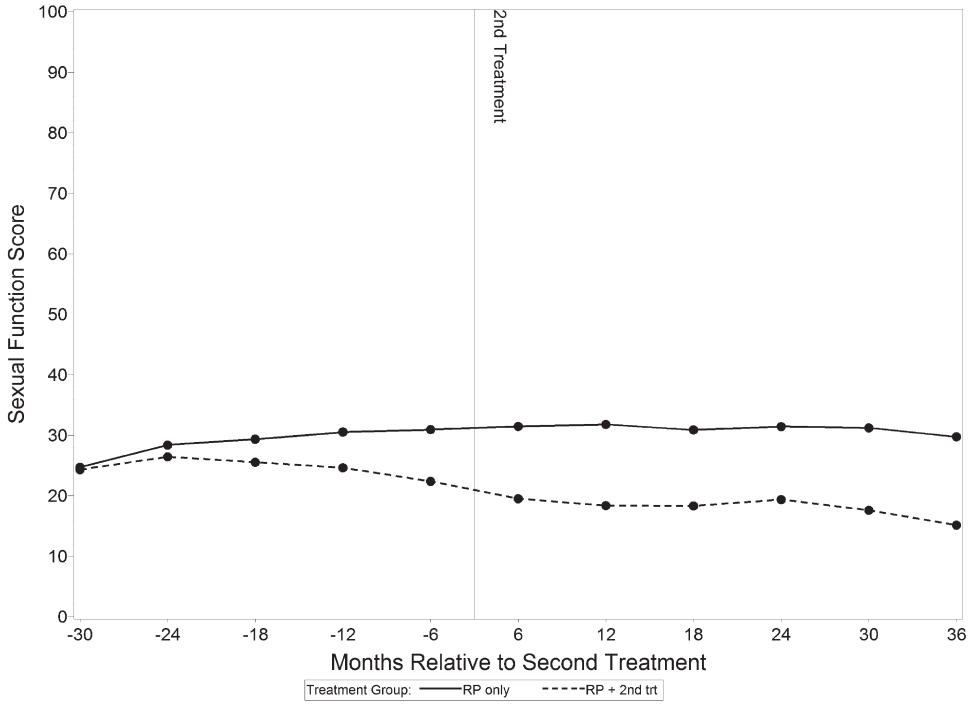

FIG. 2. Patterns of sexual function over time by treatment group

It is unclear why 15 months before second treatment appears to be the point at which the patterns of HRQOL began to diverge for the 2 groups. It could be this was the first time PSA had become detectable and that such information alone had an impact on HRQOL. With clinically relevant changes in the role-physical score and statistically significant but smaller changes in the role-emotional domain, men are beginning to see physical illness, and concomitant emotional changes impact their daily work and other activities. An increase in concern about cancer recurrence might affect the psychosocial domains of the SF-36 such as mental health, social functioning, etc. These men also are aging and likely to be experiencing some declines as a natural part of the aging process. These natural declines coupled with unrecognized disease progression may affect physical and disease specific HRQOL more than the aging process alone for men not experiencing recurrence. Finally, decline in HRQOL after second treatment may represent additive toxicity to erectile nerves and urinary sphincter from radiation or changes due to hormonal therapy.

Some limitations must be considered. This cohort of men is not a random sample and might not be representative of all men in the United States with PCa who undergo RP and then also have second treatment. Additionally, primary treatment was limited to men who underwent RP, thus limiting the generalizability.

While recognizing these limitations, this study has multiple advantages. Men from CaPSURE are sampled from more than 40 practices across the United States, which allows geographic and practice diversity. Most patients are from community based private practices, reflecting real-world variation that men with PCa may experience. In addition, we were able to study HRQOL at baseline, and before and after second treatment in men with and without that treatment.

CONCLUSIONS

Health related quality of life is not only affected after second treatment is initiated but also starts to decline approximately 1 year before second treatment. Although all domains experience a significant decrease, role-physical, sexual function, bowel bother and role-emotional have larger overall decreases, with changes in role-physical and sexual function being large enough to be of importance to patients. All aspects of HRQOL are affected and this information is vital to men with PCa who are undergoing RP. Additional counseling might be warranted since PSA recurrence could require additional treatment and further affect HRQOL.

ACKNOWLEDGMENTS

The current CaPSURE Investigators are Peter R. Carroll, MD (University of California, San Francisco, San Francisco, CA), James S. Cochran, MD (Urology Clinics of North Texas, Dallas, TX), Christopher J. Kane, MD (Veterans Administration Medical Center, San Francisco, CA), Donald P. Finnerty, MD (PAPP Clinic, Newnan, GA), Eugene V. Kramolowsky, MD (The Virginia Urology Center, Richmond, VA), Robert M. Segaul, MD (Urology Associates of West Broward Belle Terre, Sunrise, FL), Paul Sieber, MD (Urological Associates of Lancaster, Lancaster, PA), Stanley A. Brosman, MD (Pacific Clinical Research, Santa Monica, CA), Lynn W. Conrad, MD (Urology Center of the South, PC, Memphis, TN), Joseph N. Macaluso, Jr., MD, (Urologic Institute of New Orleans, Gretna, LA), Michael Flanagan, MD (Urology Specialists, Waterbury, CT), Jeffrey K. Cohen, MD (Triangle Urology Group, Pittsburgh, PA), Jerrold Sharkey, MD (Urology Health Center, New Port Richey, FL), Thomas W. Coleman, MD (Mobile Urology Group, Mobile, AL), Elliott C. Silbar, MD (Clinic of Urology, Milwaukee, WI),

Paul S. Ray, DO (Cook County Hospital, Chicago, IL), David Noyes, MD (Berkshire Urological Associates, P.C., Pittsfield, MA), Mohammed Mostafavi, MD (Urology Group of Western New England, Springfield, MA), Louis Keeler, III, MD (Center for Urologic Care, Voorhees, NJ), James Gottesman, MD (Seattle Urological, Seattle, WA), Bhupendra M. Tolia, MD (Associated Advanced Adult & Pediatric Urology, Bronx, NY), W. Lamar Weems, MD (Mississippi Urology, Jackson, MS), Glen Wells, MD (Alabama Urology, Birmingham, AL), Richard J. Kahnoski, MD (Michigan Medical, Grand Rapids, MI), Sheldon J. Freedman, MD (Las Vegas, NV), Randil Clark, MD (North Idaho Urology, Coeur D'Alene, ID), David Penson, MD, MPH (Veterans Administration Puget Sound HCS, Seattle, WA), Mark Austenfeld, MD (Kansas City Urology Care, Kansas City, MO), Henri P. Lanctin, MD (Adult & Pediatric Urology, St. Cloud, MN), J. Brantley Thrasher, MD (University of Kansas, Kansas City, KS), and David W. Bowyer, MD (Snake River Urology, Twin Falls, ID). Former CaPSURE investigators are John Forrest, MD (1995 to 1999, Urologic Specialists of Oklahoma, Tulsa, OK), William Schmeid, MD (1995 to 1999, Metro Urology, Jeffersonville, IN), Glen Brunk, MD (1995–99, Urology of Indiana, Indianapolis, IN), Jay Young, MD (1995–2001, South Orange County Medical Research Center, Laguna Woods, CA), Gary Katz, MD (1996–2000, Medical College of Virginia and Veterans Administration Medical Center, Richmond, VA), Stacy J. Childs, MD (1999–2000, Cheyenne Urological, Cheyenne, WY), Kevin Tomera, MD (1999–2001, Alaska Urological Associates, Anchorage, AK), Clayton Hudnall, MD (1995–2002, Urology San Antonio Research, San Antonio, TX).

Abbreviations and Acronyms

CaPSURE	=	Cancer of the Prostate Strategic Urological Research Endeavor
HRQOL	=	health related quality of life
PCa	=	prostate cancer
PCI	=	Prostate Cancer Index
PSA	=	prostate specific antigen
RP	=	radical prostatectomy
SF-36	=	RAND 36-Item Health Survey

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EDITORIAL COMMENT

This study unsurprisingly demonstrates that secondary therapy for biochemical recurrence after radical prostatectomy is associated with decreases in several domains of HRQOL. What is surprising and unexplained is that the decreases in HRQOL began 15 months before initiation of secondary therapy, perhaps indicating that anxiety over a newly detectable PSA affects emotional and physical functioning. Alternatively it is possible that even microscopic recurrence has an as yet undefined biological effect on well-being that has measurable physiological effects. The results highlight an under studied aspect of survivorship, and em-

phasize the global nature of the effect of a cancer diagnosis on patient sense of well-being and day-to-day functioning beyond the known physical effects of therapy. It is striking that fear of cancer recurrence persists for at least 2 years after treatment for prostate cancer.[1] Thus, it is clear that responsibility for psychological support of all patients who have undergone prostatectomy does not end with the post-operative visit.

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