Worse Urinary, Sexual and Bowel Function Cause Emotional Distress and Vice Versa in Men Treated for Prostate Cancer

Heather Orom,* Caitlin Biddle, Willie Underwood III and Christian J. Nelson

From the University at Buffalo (HO, CB) and Roswell Park Cancer Institute (WU), Buffalo and Memorial Sloan Kettering Cancer Center (CJN), New York, New York

Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer

PCa = prostate cancer

PSA = prostate specific antigen

Accepted for publication December 16, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by National Cancer Institute Grant R01#CA152425.

* Correspondence: Community Health and Health Behavior, University at Buffalo, 304 Kimball Tower, 3435 Main St., Buffalo, New York 14214 (telephone: 716-829-6682; FAX: 716-829-6040; e-mail: horom@buffalo.edu).

Purpose: Definitive therapy for prostate cancer (eg surgery or radiotherapy) often has side effects, including urinary, sexual and bowel dysfunction. The purpose of this study was to test whether urinary, sexual and bowel functions contribute to emotional distress during the first 2 years after treatment and whether distress may in turn decrease function.

Materials and Methods: The study participants were 1,148 men diagnosed with clinically localized disease who were treated with surgery (63%) or radiotherapy (37%). Urinary, sexual and bowel functions were assessed with EPIC (Expanded Prostate Cancer Index Composite). Emotional distress was assessed with the NCCN® (National Comprehensive Cancer Network®) Distress Thermometer. Assessment time points were before treatment, and 6 weeks, and 6, 12, 18 and 24 months after treatment. We used time lagged multilevel models to test whether physical function predicted emotional distress and vice versa.

Results: Men with worse urinary, bowel and sexual functions reported more emotional distress than others at subsequent time points. The relationships were bidirectional. Men who reported worse distress also reported worse urinary, bowel and sexual functions at subsequent time points.

Conclusions: Clinicians supported by practice and payer policies should screen for and facilitate the treatment of side effects and heightened emotional distress to improve well-being in survivors of prostate cancer. These interventions may be cost-effective, given that emotional distress can negatively impact functioning across life domains.

Key Words: prostatic neoplasms; stress, psychological; sexual dysfunction, physiological; urination disorders; quality of life

Patients with cancer frequently experience emotional distress, not only when they are diagnosed and during treatment but also into long-term survivorship.[1,2] Mental health issues have substantial human, medical care and other financial costs,[3,4] and interventions to reduce emotional distress in patients with cancer have been associated with decreases in care and cost savings.[5,6] Although with time emotional distress decreases in most patients with PCa, some tend to have high anxiety that does not decline to the level in the general population.[7]

Most of the 2.8 million survivors of PCa in the United States have been treated with definitive therapy, typically surgery or radiotherapy. Men treated surgically often experience some degree of urinary

0022-5347/18/1996-1464/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.12.047
Vol. 199, 1464-1469, June 2018
Printed in U.S.A.

incontinence, especially in year 1 after treatment, and most experience erectile dysfunction even 2 years postoperatively.[8] External beam radiation and brachytherapy are associated with erectile dysfunction, and bowel pain and urgency.[8,9] To understand the magnitude of the impact of treatment side effects on the lives of men, it is important to consider the impact of these side effects on emotional distress in patients with PCa treated with definitive therapy.

In a cross-sectional study of Irish survivors of PCa worse urinary function was associated with depression, anxiety and distress, and worse bowel function was associated with greater anxiety and distress.[10] Sexual function was not associated with any psychological well-being outcome. However, in an American sample greater erectile dysfunction was associated with greater depression among survivors.[11] In studies of general population samples erectile dysfunction was associated with emotional distress.[12] Rather than conceptualizing distress as the result of decreased function, in a third study it was hypothesized that psychological distress causes function declines with time.[13] The investigators found that depression and anxiety were associated with downward trends in sexual function during the 3 years after diagnosis.

The purpose of our study was to evaluate whether urinary, bowel and sexual functions affect distress and also test whether distress influences function. Our study was prospective, controlling for baseline distress and function, and men were assessed at regular intervals for the 2 years following treatment. We assessed emotional distress as well as urinary, sexual and bowel functions prior to treatment (baseline) and at 6 weeks, and 6, 12, 18 and 24 months after treatment in men who had been treated with surgery or radiotherapy (external beam radiation, brachytherapy, external beam radiation and brachytherapy or proton therapy).

METHODS

Data Source and Procedure

We used data from the Live Well Live Long! study, a prospective, multisite study of men diagnosed with clinically localized PCa. Men were recruited at or shortly after diagnosis and prior to treatment from 2 comprehensive cancer centers and 3 large group practices between 2010 and 2014. We approached 3,337 patients, of whom 2,476 were consented and 2,008 completed a baseline survey prior to treatment. We surveyed 1,679 men again 6 weeks postoperatively, and 1,638 at 6 months, 1,580 at 12 months, 1,394 at 18 months and 1,184 at 24 months. We abstracted clinical information on 1,946 men from post-treatment medical records. Data were used on 1,148 men who had available baseline data and data from at least 1 followup time point, and who had been treated with surgery or radiotherapy.

The men who completed a baseline questionnaire but were not included in multivariable models were more likely to be black than white (0.67, 95% CI 0.36–0.98, $p < 0.001$) and unmarried (−0.60, 95% CI −0.90−−0.31, $p < 0.001$), and have a lower educational attainment (−0.43, 95% CI−0.77−−0.08), lower income (−0.59, 95% CI −0.84−−0.35, $p<0.001$), worse baseline urinary function (−1.78, 95% CI 3.27−−0.30, $p = 0.019$) and worse sexual function (−3.49, 95% CI = −6.96−−0.02, $p = 0.049$).

Measures

Urinary, sexual and bowel functions were assessed with the EPIC-50 function items.[14] These items assess the frequency of being affected by a treatment related side effect during the previous 4 weeks. Scores range from 0 to 100 with higher scores indicating better function. Function variables were handled differently depending on how they were used. If they were treated as outcomes, we used raw scores. Following the recommendations by Bolger and Laurenceau,[15] function predictor variables were separated into within person and between person components.

Emotional distress was assessed with the NCCN Distress Thermometer, an 11-point 1-item visual analog scale ranging from 0—no distress to 10—extreme distress. The Distress Thermometer has been validated and it is a recommended distress screening tool in patients with PCa[16,17] with good specificity and sensitivity for detecting cancer specific distress.[18] When treated as an outcome, we used raw scores. When treated as a predictor, we calculated within person and between person components using the same method as that used for function scores.

We controlled for baseline emotional distress, and urinary, sexual and bowel functions in all models. Models were trimmed to include only additional covariates that were significantly associated with the outcome. In the untrimmed models we controlled for the type of treatment received (surgery vs radiotherapy), whether participants also received androgen deprivation therapy and the D'Amico disease risk (unpublished data). Low risk PCa was defined as clinical stage PSA 10 ng/ml or less, Gleason score 6 or less and AJCC less than cT2b.[19] Intermediate risk PCa was defined as PSA greater than 10 and 20 ng/ml or less, Gleason 7 disease or AJCC cT2b. High risk disease was defined as PSA greater than 20 ng/ml, Gleason 8-10 disease, or AJCC cT2c or higher.[19]

The demographic covariates were self-reported race/ethnicity (nonHispanic white, nonHispanic black and Hispanic, referred to as white, black and Hispanic, respectively), education attainment (a 14-level continuous variable ranging from having completed first grade to graduate school year 4), income (a 9-level variable ranging from less than $5,000 to $100,000 or greater) and patient age.

It is possible that side effects could be interpreted as signs of disease progression, in turn causing distress, rather than side effects directly causing distress. To rule out this possibility we controlled for confidence in cancer

control, which was assessed at each time point with a slightly adapted version of the cancer control subscale of the multidimensional PCa quality of life scale.[20] All categorical covariates were dummy coded and all covariates were grand mean centered.

Data Analyses

For descriptive purposes we calculated mean levels of emotional distress at each time point. We used a time lagged, multilevel model to test whether urinary, sexual or bowel function at 1 time point predicted emotional distress at the subsequent time point. An advantage of multilevel models is that cases are not deleted if they have missing data. All available data can be used to estimate effects.

Observations over time (level 1) were clustered in individuals (level 2). We hypothesized about the between and within person level 1 effects of function on distress. The first captures the effects of individual differences in urinary function on distress with time, which is when individuals with low urinary function relative to others experience more distress at the following time point relative to others. The second captures whether within individuals worse function at an earlier time point compared to average function predicts distress at a subsequent time point. We used the same analysis strategy to test whether distress predicted function.

To keep the models as parsimonious as possible we only controlled for baseline function and distress, time and covariates that were associated with the outcome variable in the untrimmed multivariable models ($p < 0.05$). Predictors were entered as fixed effects and an unstructured covariance structure was specified in all models.

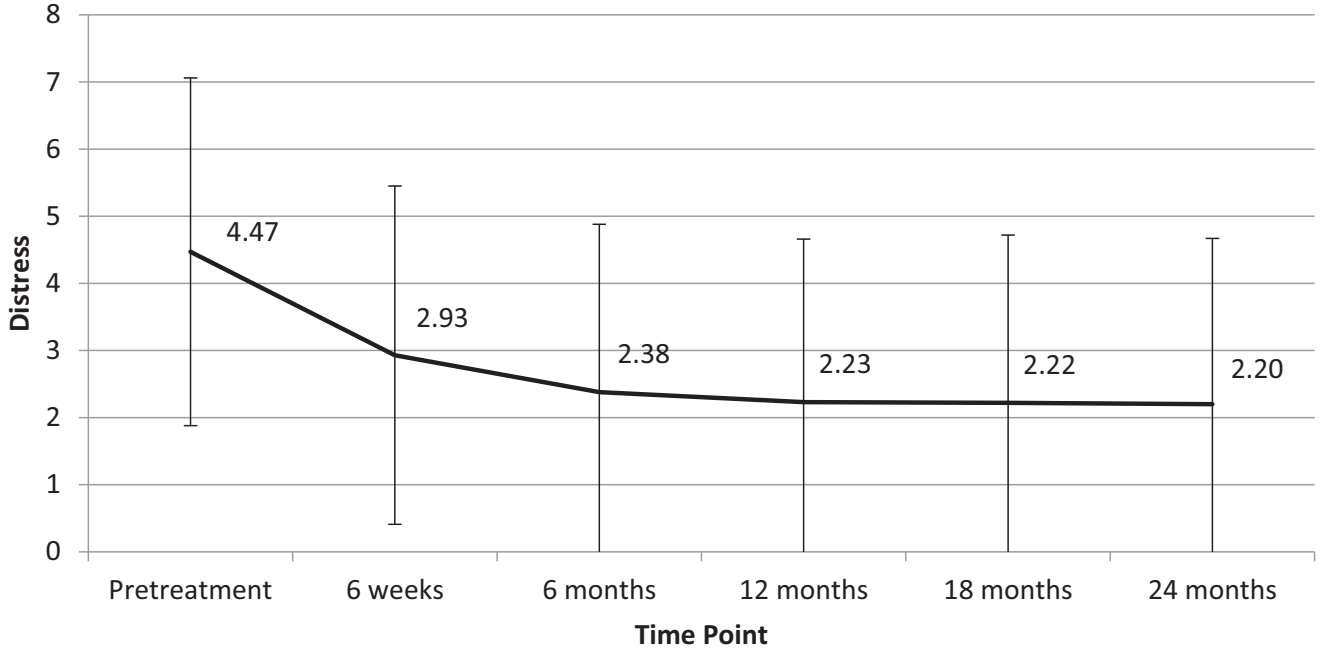
RESULTS

The supplementary table (http://jurology.com/) lists the clinical and demographic characteristics of the sample. Of the men 37% and 63% were treated with radiotherapy and surgery, respectively, and most had low or intermediate rather than high risk disease (24% and 56%, respectively, vs 20%). Our sample was 80% white, 12% black and 7% Hispanic. Of the men 55% had a college degree and most were well-off with 52% earning $100,000 per year or more.

The figure shows mean distress levels at each time point. At baseline 63% of participants scored 4 or greater on the distress scale, indicating possible clinical levels of distress. This decreased to 38% at 6 weeks, to 28% at 6 months, to 27% at 12 months, to 26% at 18 months and to 27% at 24 months.

In the model testing whether function predicts emotional distress the between person effects of urinary, sexual and bowel functions on distress were significant (see table). On average the individuals with worse urinary function ($b = -0.03$, SE 0.004, 95% CI -0.03–-0.02), worse sexual function ($b = -0.01$, SE 0.003, 95% CI -0.02–-0.007) and worse bowel function ($b = -0.07$, SE 0.008, 95% CI -0.08–-0.05, all $p < 0.001$) were more emotionally distressed at the followup time points than men with better function.

None of the within person effects of function on distress were significant. Greater confidence in cancer control at a previous time point was associated with lower emotional distress at the following



Mean distress at each time point. Bars indicate SD.

Effects of urinary, sexual, and bowel function on distress in 1,146 men, and effects of distress on urinary function in 1,137, sexual function in 1,103 and bowel function in 1,148

Effects	b	SE	95% CI	p Value
Urinary, sexual + bowel function effect on distress				
Urinary function:*				
Within person	−0.002	0.003	−0.007−0.004	0.569
Between person	−0.03	0.004	−0.03−−0.02	<0.001
Sexual function:*				
Within person	−0.003	0.003	−0.008−0.002	0.314
Between person	−0.01	0.003	−0.02−−0.007	<0.001
Bowel function:*				
Within person	0.01	0.004	−0.001−0.02	0.070
Between person	−0.07	0.008	−0.08−−0.05	<0.001
Ca control†	−0.02	0.002	−0.02−−0.01	<0.001
Baseline:†				
Distress	0.27	0.02	0.23−0.31	<0.001
Urinary function	−0.002	0.005	−0.01−0.01	0.650
Sexual function	0.003	0.003	−0.003−0.008	0.332
Bowel function	0.02	0.007	0.004−0.03	0.013
Time	−0.02	0.03	−0.08−0.03	0.438
Education†	0.02	0.02	−0.01−0.06	0.242
Age†	−0.05	0.008	−0.06−−0.03	<0.001
Distress effect on urinary function				
Distress:*				
Within person	−0.19	0.09	−0.36−−0.02	0.029
Between person	−2.51	0.21	−2.92−−2.09	<0.001
Ca control†	0.03	0.01	0.01−0.05	0.008
Baseline:†				
Distress	0.75	0.16	0.43−1.08	<0.001
Urinary function	0.28	0.04	0.20−0.35	<0.001
Time	0.86	0.12	0.63−1.09	<0.001
Age†	−0.26	0.06	−0.37−−0.15	<0.001
Radiotherapy‡	9.37	1.00	7.41−11.33	<0.001
NonHispanic black‡	−3.62	1.19	−5.95−−1.29	0.002
High risk‡	−3.64	0.97	−5.54−−1.75	<0.001
Distress effect on sexual function				
Distress:*				
Within person	−0.24	0.13	−0.50−0.01	0.059
Between person	−2.27	0.29	−2.84−−1.70	<0.001
Ca control†	0.04	0.01	0.01−0.07	0.005
Baseline:†				
Distress	0.93	0.23	0.49−1.37	<0.001
Sexual function	0.52	0.02	0.47−0.57	<0.001
Time	1.48	0.17	1.15−1.82	<0.001
Education†	0.56	0.19	0.20−0.92	0.003
Age†	−0.47	0.08	−0.64−−0.31	<0.001
Radiotherapy†§	8.80	1.50	5.85−11.75	<0.001
Hormone therapy†§	−9.08	1.77	−12.54−−5.62	<0.001
Risk:§				
Intermediate	−4.29	1.28	−6.80−−1.79	0.001
High	−9.66	1.69	−12.98−−6.34	<0.001
Distress effect on bowel function				
Distress:*				
Within person	−0.03	0.07	−0.16−0.11	0.685
Between person	−1.11	0.11	−1.32−−0.91	<0.001
Ca control†	0.03	0.01	0.02−0.04	<0.001
Baseline:†				
Distress	0.30	0.08	0.14−0.46	<0.001
Bowel function	0.42	0.02	0.38−0.46	<0.001
Time	−0.01	0.09	−0.19−0.16	0.879
Age†	−0.07	0.03	−0.13−−0.02	0.005
Radiotherapy†‖	−2.81	0.43	−3.66−−1.96	<0.001

* Time lagged predictor variables.
† Grand mean centered covariates.
‡ Referents surgery, nonHispanic white and low risk.
§ Referents surgery, no hormone therapy and low risk.
‖ Referent surgery.

time point (b = −0.02, SE 0.002, 95% CI −0.02−−0.01, p <0.001). Higher baseline distress and higher baseline bowel function were associated with greater distress with time (b = 0.27, SE 0.02, 95% CI 0.23−0.31, p <0.001 and b = 0.02, SE 0.007, 95% CI 0.004−0.03, p = 0.013, respectively). Older participants were also less distressed (b = −0.05, SE 0.008, 95% CI −0.06−−0.03, p <0.001).

In the reversed models in which we tested whether emotional distress affects function the men with higher emotional distress at 1 time point experienced worse urinary function (b = −2.51, SE 0.21, 95% CI −2.92−−2.09), sexual function (b = −2.27, SE 0.29, 95% CI −2.84−−1.70) and bowel function (b = −1.11, SE 0.11, 95% CI −1.32−−0.91, all p <0.001) 6 months later compared to those with lower emotional distress (see table). There was also a within person effect of more emotional distress on worse urinary function (b = −0.19, SE 0.09, 95% CI −0.36−−0.02, p = 0.029), suggesting that a man who experienced more than his average distress at 1 time point experienced worse urinary function at the subsequent time point. The table lists associations between covariates and function.

Men on active surveillance were not included in our analyses. However, the bidirectional relationship between function and distress held for this group as well. There were significant between person effects of urinary, sexual and bowel functions on distress (p <0.034). There were significant between person effects of distress on urinary, sexual and bowel function (p ≤0.001) and an additional within person effect of higher distress associated with better bowel function (p = 0.028).

DISCUSSION

During the 2 years after being treated with surgery or radiotherapy men with worse urinary, sexual and bowel functions compared to their counterparts experienced more emotional distress at subsequent time points. The reverse relationship was also true since being more emotionally distressed than their counterparts predicted worse function at a subsequent time point.

This bidirectional relationship likely affects PCa survivors because of the risk of urinary, sexual and bowel side effects of PCa treatment but it is not specific to PCa survivors. The relationship between depression and sexual dysfunction has been bidirectional in general population samples.[21] Anxiety and depression are also related to bowel function.[22]

While we might easily understand how living with side effects of PCa treatment could be distressing, it is less obvious how distress might cause decrements in physical functioning. There is evidence that emotional distress influences perceptions of the

severity of physical symptoms.[23] Emotional distress could also influence urinary, bowel and sexual functions via physiological pathways,[24,25] compounding the effects of treatment side effects. Also, some medications used to treat depression or anxiety such as serotonin reuptake inhibitors, which we did not assess, can cause sexual and bowel dysfunction.

We found across the board, between person effects of functioning and distress but only a statistically significant within person effect of distress on urinary function, although the within person effects of distress on sexual function was marginally significant. Within person effects capture within person variability around an individual mean. We might expect variations in distress and functioning to cycle relatively rapidly, perhaps in days or weeks rather than months. Since we only assessed the men every 6 months, we likely missed capturing any existing relationship between fluctuations in distress and corresponding changes in functioning or vice versa.

Emotional distress levels in our sample followed the general pattern reported previously in the literature, in which emotional distress is highest at diagnosis and subsequently decreases.[7,18,26] Typically about a quarter to a third of men experience clinically significant emotional distress and can continue to experience psychological issues throughout survivorship.[7,27] Our rates were somewhat higher, particularly at baseline, perhaps because the Distress Thermometer may overestimate clinically significant distress.[28]

The Distress Thermometer is a recommended screening tool for emotional distress in cancer survivors. However, longer scales such as BDI-II (Beck Depression Inventory-II) and HADS (Hospital Anxiety and Depression Scale) are the gold standard to identify patients with anxiety or depression. If the goal is to identify precisely what levels of dysfunction may result in clinically significant distress, a more psychometrically robust measure of emotional distress should be used.

Also, while we controlled for baseline emotional distress, it would be informative to control for trait anxiety, neuroticism and comorbid anxiety, and depression to understand how much of the association between urinary, bowel or sexual functioning and distress are attributable to personal differences in these characteristics. However, knowing the extent that is attributable to personality traits or baseline psychological issues would not radically change the approach to intervention.

We may have underestimated the strength of the relationships between function and distress due to the relatively higher attrition among participants with worse urinary and sexual function, although not higher distress, as well as those who were most likely to be underserved (eg unmarried or minority men). Our findings underline the importance of screening for distress, monitoring for treatment side effects, and providing interventions for emotional distress and side effects when indicated.

Finally, our results are important to clarify the causal relation between side effect related physical functioning and emotional distress. To our knowledge our study provides the strongest evidence to date that the relationship between the 2 factors is bidirectional.

CONCLUSIONS

It has been argued that reducing the emotional burden of cancer is feasible and cost-effective.[29] It is not simply adequate to monitor patients with cancer for distress and physical quality of life issues.[30] Intervention must be accessible. While this might include greater investment in psychosocial care, for PCa care it also means mitigating survivor treatment side effects. As most patients with PCa have an excellent prognosis, the primary long-term sequelae of the disease are the side effects of treatment. Two health policy changes that could improve survivor well-being are increased access to health care coverage for treatments of erectile dysfunction and better access to psycho-oncologic care at diagnosis and after treatment in men who have high distress. Also, given the likely bidirectional nature of the relationship between side effects and emotional distress, it makes sense for facilities that have traditionally not incorporated psychosocial care into practice to consider doing so.

REFERENCES

1. Bill-Axelson A, Garmo H, Holmberg L et al: Long-term distress after radical prostatectomy versus watchful waiting in prostate cancer: a longitudinal study from the Scandinavian Prostate Cancer Group-4 randomized clinical trial. Eur Urol 2013; **64:** 920.
2. Krebber AMH, Buffart LM, Kleijn G et al: Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 2014; **23:** 121.
3. Luppa M, Heinrich S, Angermeyer MC et al: Cost-of-illness studies of depression. A systematic review. J Affect Disord 2007; **98:** 29.
4. Simon GE: Social and economic burden of mood disorders. Biol Psychiatry 2003; **54:** 208.
5. Simpson JSA, Carlson LE and Trew ME: Effect of group therapy for breast cancer on healthcare utilization. Cancer Pract 2001; **9:** 19.
6. Sabariego C, Brach M, Herschbach P et al: Cost-effectiveness of cognitive-behavioral group therapy for dysfunctional fear of progression in cancer patients. Eur J Health Econ 2011; **12:** 489.

7. Korfage IJ, Essink-Bot ML, Janssens AC et al: Anxiety and depression after prostate cancer diagnosis and treatment: 5-year follow-up. Br J Cancer 2006; **94:** 1093.
8. Donovan JL, Hamdy FC, Lane JA et al: Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016; **375:** 1425.
9. 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.
10. Sharp L, O'Leary E, Kinnear H et al: Cancer-related symptoms predict psychological well-being among prostate cancer survivors: results from the PiCTure study. Psychooncology 2016; **25:** 282.
11. Nelson CJ, Mulhall JP and Roth AJ: The association between erectile dysfunction and depressive symptoms in men treated for prostate cancer. J Sex Med 2011; **8:** 560.
12. Araujo AB, Durante R, Feldman HA et al: The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med 1998; **60:** 458.
13. Punnen S, Cowan JE, Dunn LB et al: A longitudinal study of anxiety, depression and distress as predictors of sexual and urinary quality of life in men with prostate cancer. BJU Int 2013; **112:** E67.
14. 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.
15. Bolger N and Laurenceau JP: Intensive Longitudinal Methods: An Introduction to Diary and Experience Sampling Research. New York: Guilford Press 2013.
16. Roth AJ, Kornblith AB, Batel-Copel L et al: Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 1998; **82:** 1904.
17. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Fort Washington, Pennsylvania: National Comprehensive Cancer Network 2012; vol 2014.
18. Chambers SK, Zajdlewicz L, Youlden DR et al: The validity of the distress thermometer in prostate cancer populations. Psychooncology 2014; **23:** 195.
19. 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.
20. Clark JA, Bokhour BG, Inui TS et al: Measuring patients' perceptions of the outcomes of treatment for early prostate cancer. Med Care 2003; **41:** 923.
21. Atlantis E and Sullivan T: Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. J Sex Med 2012; **9:** 1497.
22. Henningsen P, Zimmermann T and Sattel H: Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. Psychosom Med 2003; **65:** 528.
23. Pennebaker JW: The Psychology of Physical Symptoms. New York: Springer-Verlag 1982.
24. Lovallo WR: Stress and Health: Biological and Psychological Interactions. Thousand Oaks, California: Sage 2015.
25. Zorn BH, Montgomery H, Pieper K et al: Urinary incontinence and depression. J Urol 1999; **162:** 82.
26. Dale W, Bilir P, Han M et al: The role of anxiety in prostate carcinoma: a structured review of the literature. Cancer 2005; **104:** 467.
27. Halbert CH, Coyne J, Weathers B et al: Racial differences in quality of life following prostate cancer diagnosis. Urology 2010; **76:** 559.
28. Mitchell AJ: Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol 2007; **25:** 4670.
29. Carlson LE and Bultz BD: Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses. Psychooncology 2004; **13:** 837.
30. Hollingworth W, Metcalfe C, Mancero S et al: Are needs assessments cost effective in reducing distress among patients with cancer? A randomized controlled trial using the Distress Thermometer and Problem List. J Clin Oncol 2013; **31:** 3631.