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Depressive symptoms before treatment predict disease specific quality of life six months after treatment among patients with localized prostate cancer

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Abstract

Purpose—This study examined whether depressive symptoms before localized prostate cancer treatment predict disease specific quality of life (i.e., sexual and urinary dysfunction, sexual and urinary bother, and activity limitation due to urinary dysfunction) reported six months following treatment among newly diagnosed patients.

Materials and Methods—A case series of patients recently diagnosed with localized prostate cancer (T1-2N0M0) at FCCC were eligible. Of the 1370 eligible patients, 869 (63.34%) completed questionnaires at diagnosis (baseline) and six months following treatment. Patients were treated with surgery (16.8%), brachytherapy (27.6%), or external beam radiation (55.6%). Depressive symptoms and disease specific quality of life were assessed with established measures (i.e., Center for Epidemiologic Studies Depression Scale (CES-D); sexual adjustment questionnaire (SAQ); and the American Urological Association symptom index).

Results—A fifth of the sample (19.7%) reported clinically elevated levels of depression. All aspects of disease specific QOL decreased significantly between baseline and six months following treatment. Depressive symptoms at baseline significantly predicted sexual and urinary dysfunction, related bother, and activity limitation due to urinary dysfunction at 6-month controlling for age, PSA level, Gleason score, treatment type, and relevant baseline indicators of sexual and urinary dysfunction, related bother and activity limitation ($p < .05$).

Conclusions—Depressive symptoms before prostate cancer treatment predict disease-specific quality of life after treatment. Health care providers should be sensitive to the display of depressive symptoms before treatment and consider preventative interventions including at the

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least, preparing patients for the changes in disease-specific QOL and related bother following prostate cancer treatment.

Introduction

Prostate cancer diagnosis and treatment are associated with increased depression and psychological distress among patients.¹⁻³ Research however, also showed inconsistency in the levels of depression reported.¹⁻⁵ The prevalent rates of clinically significant levels of depression reported range from 11% to 37%.¹⁻⁶ Although, levels of depression decrease significantly after treatment, this might not be the case for all patients.⁵ Indeed, it is likely that patients who experience depressive symptoms after diagnosis also experience depressive symptoms and lower levels of quality of life in general after treatment.^{5,7} For example a population based cohort study of urological symptoms, sexual functioning and quality of life among men 50 years or older has demonstrated that men with depressive symptoms were at 2.8 times higher risk (95% CI 1.5–5.2) for moderate or severe nocturia than those without depressive symptoms.⁸ No study, however, has examined associations between pre-treatment depressive symptoms and disease specific QOL (i.e., sexual and urinary dysfunction and related bother) following treatment among patients with prostate cancer. The present study aims to address this issue by using a prospective longitudinal design to explore relationships between pre-treatment depressive symptoms and post-treatment urinary and sexual function six months following prostate cancer treatment. It is hypothesized that higher levels of pre-treatment depressive symptoms will be associated with lower levels of disease specific QOL (i.e., urinary and sexual functioning).

PATIENTS AND METHODS

Procedure and inclusion/exclusion criteria

The present study was part of an IRB approved longitudinal investigation examining QOL among patients diagnosed with localized prostate cancer.⁹ Participants were cancer patients (T1-2N0M0) who presented for a second opinion about treatment options.¹⁰ Eligibility criteria were: a) patients have a diagnosis of localized prostate cancer during the past 4 to 6 weeks, b) fluency in English, and c) lack of serious co-existent diseases that limit patients' treatment options as prostatectomy is not recommended for men with health complications such as diabetes and cardiovascular diseases.¹¹ Collaborating physicians introduced the study to eligible patients and obtained permissions for study personnel to contact potentially eligible patients. If patients agreed to be contacted, they were telephoned, the study was discussed in detail, and an informed consent form and the baseline questionnaire (t1) were mailed out. Additional questionnaires were mailed at six months (t2) after baseline assessment.¹²⁻¹⁴ A stamped, self-addressed return envelope was provided with questionnaires and patients received \$10 for returning questionnaires. Data from patients who responded to the two measurement points were included in the analyses.

Of the 1370 referred eligible patients, 986 completed and returned the baseline questionnaire (t1; 72% acceptance and return rate). Of those ($n = 923$) 93.6 percent returned the 6-month (t2) questionnaire (Table 1 for assessment used). All patients had completed their initial prostate cancer treatment prior to the 6-month assessment (t2). Of the 923 patients who

completed the baseline assessment, 483 (52.3%) opted for 3-dimensional conformal radiation therapy, 240 (26%) had brachytherapy, 146 (15.8%) had prostatectomy, 70 patients (24.6%) received neoadjuvant therapy and 39 patients received adjuvant therapy (4.9%; see Table 2). Only 48 patients (5.2%) have chosen watchful waiting and six patients opted for hormone therapy as a primary treatment (0.7%). These 54 patients were subsequently removed from the predictive analyses because cell sizes were too small to conduct meaningful statistical analyses (i.e., hormonal therapy). Thus, the current analyses are based on the 869 (63.43%) patients who completed the baseline (t1) and the 6-month assessments (t2) and were treated with prostatectomy, external beam radiation, or brachytherapy.

Dropout Analyses

To examine any potential bias introduced through selective attrition, we compared patients who completed the two assessments ($n = 923$) with patients who dropped out of the study ($n = 63$) on demographic and clinical variables. Results showed significant differences indicating that patients who dropped out were more likely to be younger, not married, employed, or belonged to African American, Latino, or other ethnic minority compared to patients who completed the two assessments ($ps < .05$). Patients with complete follow-up information ($N = 923$) were on average 65.45 years old ($SD = 7.57$, range 39- 83 years), Caucasians (90.6%), married (81.8%), had either college education or post-graduate education (48.9 %), or were not employed at the time of the baseline assessment (57.6%). At the time of diagnosis, the average PSA level was 7.53 ng/mL ($SD = 7.08$; range: 0 – 70). The majority of patients (73.2%) had a Gleason score of less than seven (see Table 2).

Sociodemographic and health-related measures

To reduce participant burden, short versions of established scales were used to assess study outcomes. The baseline questionnaire included demographic (e.g., age, ethnicity, marital status, employment, education), medical variables (e.g., PSA level, Gleason score), a depression scale, and scales assessing disease specific quality of life (urinary and sexual dysfunction, urinary and sexual bother, and activity limitation due to urinary dysfunction). QOL measures were administered also at six months.¹²⁻¹⁴ Depressive symptoms were assessed with the 11-item depression scale (CES-D)¹² A summed score of 9 was used as cut-off value to indicate clinically elevated levels of depressive symptoms.¹⁵⁻¹⁶ All scales, number of items, item response, and Cronbach's alphas are depicted in Table 1. Higher scores indicate higher levels of depressive symptoms, urinary and sexual dysfunction, bother, and activity limitation due to urinary dysfunction.

Statistical analysis

Data were analyzed with the statistical software.¹⁷ Repeated Measures ANOVA were used to examine changes of QOL measures and possible interaction between time and treatment modality. Multiple regression analyses were used to examine potential effects of baseline depressive symptoms on disease-specific QOL at six months controlling for potential demographic and clinical covariates (i.e., age, dummy coded marital status (married = 1, not married = 0), educational level (college or above = 1, high school or below = 0),

neoadjuvant or adjuvant hormone therapy (yes =1, no = 0), PSA level, Gleason score, and treatment modality and baseline measures of QOL.

RESULTS

The mean value of depressive symptoms at baseline was 5.11 ($SD = 4.42$; range 0 – 27); however, a fifth of the sample (i.e., 19.7%) reported clinically elevated levels of depressive symptoms (i.e., a CES-D score of ≥ 9)^{15–16}. Patients reported moderate levels of sexual problems and bother due to sexual problems, few problems with urinary function and low levels of bother and activity limitations due to urinary dysfunction at baseline (see Table 3). At baseline EBRT group reported higher levels of urinary and sexual dysfunction and urinary and sexual bother compared to both surgery and brachytherapy groups. However, at 6 months, brachytherapy patients reported significantly higher levels of urinary dysfunction, bother and limitations compared to the surgery and EBRT groups. Sexual dysfunction was highest among surgery patients compared to both EBRT and brachytherapy patients (All $p < .05$; Table 3)

Repeated measures ANOVA revealed a significant increase in sexual dysfunction ($F(1, 781) = 239.57, p < .001, \eta^2 = .24$) and in sexual bother between the baseline and six months assessments ($F(1, 694) = 1134.74, p < .001, \eta^2 = .16$). Significant interaction effects between time and treatment modality were found for both sexual dysfunction ($F(2, 781) = 15.55, p < .001, \eta^2 = .04$) and sexual bother ($F(2, 694) = 28.12, p < .001, \eta^2 = .10$) indicating that the increase was substantial for patients treated with prostatectomy compared to those treated with external beam radiation or brachytherapy (see Table 3). Similarly, we found a significant increase in urinary problems between baseline and six months ($F(1, 835) = 43.47, p < .001, \eta^2 = .05$). Results also showed a main effect of treatment modality ($F(2, 835) = 3.64, p < .05, \eta^2 = .01$) and a significant interaction between time and treatment modality ($F(2, 835) = 51.31, p < .001, \eta^2 = .11$) indicating that patients who had brachytherapy were more likely to report higher levels of urinary dysfunction and an increase in urinary problems between the baseline and six months assessments compared to patients who had surgery or external beam radiation therapy (Table 3).

Using ANOVA we found a significant increase in bother due to urinary problems ($F(1, 817) = 84.31, p < .001, \eta^2 = .09$) and activity limitation attributed to urinary problems ($F(1, 802) = 53.02, p < .001, \eta^2 = .06$). ANOVA results demonstrated a significant interaction between time and treatment modality for both urinary bother ($F(2, 817) = 30.12, p < .001, \eta^2 = .07$) and activity limitation due to urinary problems ($F(2, 802) = 18.99, p < .001, \eta^2 = .05$) suggesting that the increase in urinary bother and limitation were substantial for patients treated with brachytherapy compared to those treated with external beam radiation or surgery (Table 3).

Depressive symptoms, sexual dysfunction, and sexual bother

We computed a series of five linear regression analyses to explore the effect of baseline depressive symptoms on different aspects of disease-specific quality of life. In each case, we controlled for baseline QOL levels, (e.g., sexual dysfunction), and age, marital status, educational level, PSA level, Gleason score, dummy-coded hormone therapy and treatment

modality. To compare between treatment types, two dummy coded treatment variables were included with the external beam radiation treatment as the references group. Results showed that, in each statistical model, baseline levels of depressive symptoms significantly predicted disease specific QOL (i.e., sexual dysfunction, sexual bother, urinary dysfunction, urinary bother, and urinary limitation) six months later. Table 4 shows standardized regression coefficient of all predictors and total, degree of significance, and total variance explained by all predictors (See Table 4: Models 1, 2, 3, 4 & 5).

DISCUSSION

A prostate cancer diagnosis is often times accompanied by significant levels of depression and psychological distress.¹⁻⁵ Data from a prospective study gave us an unprecedented opportunity to examine the impact and the direction of the relationship between pre-treatment depressive symptoms and post-treatment disease specific QOL over a 6-month period following diagnosis and treatment. Results confirmed the study hypothesis that pretreatment depressive symptoms have a significant and negative relationship to post-treatment disease specific QOL, controlling for baseline levels of clinical and demographic variables and disease specific QOL.

Mirroring other findings in the literature our results showed that disease specific quality of life decreased significantly following prostate cancer treatment, specifically for patients who had surgery. Sexual dysfunction and sexual bother increased significantly over the six months among all patients, particularly among patients treated with surgery compared to patients treated with external beam radiation or brachytherapy. Similarly urinary dysfunction, bother due to urinary dysfunction, and activity limitation due to urinary dysfunction increased significantly over the 6-month period. Confirming other reports in the literature, this increase among these outcomes was significantly higher among patients who had brachytherapy compared to patients who had surgery or radiation therapy.¹⁸ As expected, older age and receiving adjuvant or neoadjuvant hormone treatment was significantly associated with a decline in sexual function and increases in sexual bother at 6 months following treatment.¹⁹

Increases in urinary and sexual dysfunction, related bother, and activity limitation due to urinary dysfunction are generally considered to be a treatment-related complication.¹¹ Our results, however, indicated that those who reported higher levels of depressive symptoms at the time of diagnosis (i.e., before treatment) were significantly more likely to experience increased levels of sexual and urinary dysfunction, related bother, and activity limitation due to urinary dysfunction at six months. Our results are in line with previous studies conducted with non-prostate cancer patients which reported that elevated levels of psychological distress before surgery were significantly associated with poorer post-surgery outcomes.²⁰⁻²³ Our results are also consistent with a recent study that found an association between untreated depressive symptoms and an increased incidence of moderate to severe nocturia among elderly men.⁸ The biological mechanism underlying the relationship between depressive symptom and disease-specific QOL in our study is unclear and warrants further investigation. It is possible that psychosocial mechanisms, such as elevated reporting of dysfunction and bother contribute to the depressive symptoms-sexual dysfunction

relationships. Previous research also suggests that depressed prostate cancer patients may be less likely to use assistive sexual aids (e.g., vacuum erection devices) following prostate cancer treatment which might increase sexual bother and, thus, in turn, increase depressive symptoms.²⁵⁻²⁶ In addition, sexual dysfunction and sexual bother is often considered part of the depressive symptom complex.²⁴ This mechanisms has been reported by De Berardis and colleagues (2008) who demonstrated that increased depressive symptoms preceded the onset of ED among patients with Type 2-diabetes.²⁴ While this possible explanation for the relationship between pretreatment depressive symptom and sexual dysfunction and bother cannot be ruled out here, it would not account for the relationships to other outcomes (e.g., urinary problems).

Limitations and Suggestions for Future Research

Although the study design is longitudinal, the time lag between baseline and 6-month assessments is relatively brief and does not allow for examining the long-term side effects of prostate cancer treatment. However, we believe that the quality of life aspects that we examined (i.e., sexual and urinary dysfunction) are important for all patients at any time as they cope with prostate cancer and its treatment. In addition, the possibility that one could reduce the early impact of post-treatment side effects for a significant portion of patients who experience elevated levels of depressive symptoms prior to prostate cancer treatment is important to consider. Early tailored interventions to reduce pre-treatment depression might be appropriate to help patients cope with the short-term treatment side effects and reduce the burden of the disease on both patients and their families. Another limitation of the study is that the sample consists mainly of Caucasian patients with an identifiable social support structure (i.e., being married) and a high percentage of retired patients. Thus, our findings might not apply to patients with different social characteristics. It will be of interest in future research to explore the possibility that the relationships reported here will be more pronounced in a setting with higher levels of depressive symptoms and greater underlying risk of symptoms.

CONCLUSION

Results of this prospective longitudinal study indicate that elevated levels of pre-treatment depressive symptoms are predictive of increased levels of disease-specific QOL indicators and functioning-related bother and activity limitation 6-months post-diagnosis. Health care providers may want to be sensitive to the signs of depressive symptoms among prostate cancer patients and consider intervening to ameliorate common post-treatment symptomatology and to increase disease-specific QOL.

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Table 1

Measurements of central variables of the study

Measurement	scales	Item#	Item example	Items' response range	Chronbach's Alpha
Depressive symptoms	Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977)	11	"I felt sad"	rarely (0) to most of the time (3)	.88
Sexual dysfunction	Sexual Adjustment Questionnaire (SAQ; Waterhouse, 1986)	3	"were you able to get and keep an erection when sexually excited"	not at all (1) to very much (5)	.67
Sexual bother	Sexual Adjustment Questionnaire (SAQ; Waterhouse, 1986)	1	"how bothersome sexual problems have been"	not at all (1) to very much (5)	--
Urinary dysfunction	The American Urological Association symptom index (AUA; Barry et al., 1992)	3	"had frequent day time urination been a problem"	not at all (1) to very much (5)	.73
Urinary bother	The American Urological Association symptom index (AUA; Barry et al., 1992)	1	"how bothersome problems with urination have been"	not at all (1) to very much (5)	--
Urinary-related activity limitation	The American Urological Association symptom index (AUA; Barry et al., 1992)	1	"have urinary problems e kept you from doing things"	not at all (1) to very much (5)	--

Table 2

Descriptive statistics of demographic and clinical characteristics by treatment type

Characteristics	Prostatectomy (n = 146, 16.8%)	EBRT (n = 483, 55.6%)	Brachytherapy (n = 240, 27.6%)	Full Sample (N = 869)	χ^2/F	p
Age (Mean \pm SD)	58.38 \pm 6.70 ^a	67.24 \pm 6.91 ^b	66.16 \pm 6.84 ^b	65.45 \pm 7.57	95.14	.001
PSA Level (Mean \pm SD)	5.99 \pm 3.41 ^a	8.77 \pm 8.59 ^b	6.13 \pm 4.27 ^c	7.53 \pm 7.08	14.724	.001
Gleason Score (Mean \pm SD)	6.14 \pm .70 ^a	6.40 \pm .86 ^b	6.01 \pm .37 ^a	6.3 \pm 0.8	21.04	.001
Received neo-adjuvant/adjuvant	6.8%	12.6%	16.2%	13%	7.25	.03
<u>Education:</u>						
High School	47.2%	48.1%	59.6%	51.1%	1.93	.38
College	52.8%	51.9%	40.4%	48.9%		
<u>Marital Status:</u>						
Married/with partner	78.8%	82%	83.3%	81.8%	1.29	.52
Single/Widowed/Divorced	21.2%	18%	16.7%	18.2%		
<u>Race</u>						
Caucasian	90.4%	89.9%	92.1%	90.6%	10.43	.23
African American	8.2%	7.9%	5.8%	7.4%		
Hispanic	1.4%	.8%	1.7%	1.2%		
Asian/Other	0%	1.4%	0.4%	.9%		
<u>Employment</u>						
Employed	69.9%	33.5%	30.4%	57.6%	72.07	.001
Not employed/retired	30.1%	66.5	69.6%	42.4%		

Note. Different letters indicate significant differences between groups. Similar letters indicate the lack of significant differences between groups. Total sample is not included in statistical comparisons between the three treatment groups; surgery, radiation, and brachytherapy.

Table 3

Comparison between treatment groups in study outcomes at baseline (t1) and at six months (t2)

Study Outcomes	Surgery (n = 146)		EBRT (n = 483)		Brachytherapy (n = 240)		Total sample (N = 869)		F	p
	M±SD		M±SD		M±SD		M±SD			
Depressive symptoms t1	5.87±3.94 ^a		4.95±4.73 ^b		5.02±4.43 ^b		5.13±4.52		3.28	.04
High levels of depressive symptoms t1	27.4%		19.3%		19.4%		19.7%		X ² = 8.3	.02
Low levels of depressive symptoms t1	72.6%		79.9%		80.6%		80.3%			
Urinary dysfunction t1	1.73±.82		1.87±.85 ^a		1.63±.70 ^b		1.78±.81		5.715	.003
Urinary dysfunction t2	1.77±.85 ^a		1.85±.80 ^a		2.36±.99 ^b		1.98±.90		23.89	.001
Urinary bother t1	1.61±.83		1.78±.97 ^a		1.47±.76 ^b		1.67±.90		5.71	.001
Urinary bother t2	1.99±1.08 ^a		1.84±.90 ^a		2.26±1.12 ^b		1.97±1.02		13.69	.001
Urinary limitation t1	1.17±.53		1.24±.62		1.09±.36		1.19±.55		2.70	.07
Urinary limitation t2	1.37±.74		1.24±.58 ^a		1.52±.99 ^b		1.34±.75		8.85	.001
Sexual dysfunction t1	2.10±.87 ^a		2.51±.93 ^b		2.38±.88 ^a		2.40±.92		9.70	.001
Sexual dysfunction t2	2.93±.73		2.84±1.02		2.86±1.07		2.86±.99		1.73	.18
Sexual bother t1	1.89±1.08 ^a		2.38±1.28 ^b		2.20±1.21		2.25±1.24		6.46	.001
Sexual bother t2	3.35±1.16 ^a		2.53±1.21 ^b		2.67±1.25 ^b		2.71±1.25		24.40	.001

Note. Different letters indicate significant differences between groups. Similar letters indicate the lack of significant differences between groups. Total sample is not included in statistical comparisons between the three treatment groups; surgery, radiation, and brachytherapy.

Table 4

Standardized co-efficient of baseline (t1) predictors of disease-specific QOL at six months (t2)

Baseline (t1) predictors of Disease specific QOL at 6 Months (t2)	Disease specific QOL at 6 Months (t2)				
	Model 1: Predicting sexual dysfunction at 6-month (t2)	Model 2: Predicting sexual bother at 6-month (t2)	Model 3: Predicting urinary dysfunction at 6-month (t2)	Model 4: Predicting urinary bother at 6-month (t2)	Model 5: Predicting urinary limitation at 6-month (t2)
Age	.10****	-.02	.02	.01	.06
Marital status	-.05	-.03	-.06 [†]	.01	.01
Education level	.03	-.01	-.02	-.04	-.01
Employment	.08*	.02	.01	.01	.02
PSA Level	.07 [†]	-.04	.05	.03	.01
Gleason Score	.05	.05	.01	.03	.00
Surgery (dummy coded)	-.31****	-.37****	.01	.09*	-.03
Brachytherapy (dummy coded)	-.19****	-.28****	.29****	.25****	.19****
Neoadjuvant or adjuvant	.11**	.10**	.05 [†]	.06 [†]	.02
Depressive symptoms at baseline (t1)	.07*	.13**	.14****	.15*	.18****
Sexual Dysfunction at baseline (t1)	.49****				
Sexual Bother at baseline (t1)		.30****			
Urinary Dysfunction at baseline (t1)			.47****		
Urinary Bother at baseline (t1)				.34****	
Urinary Limitation at baseline (t1)					.27****
R²_{Total}	.36	.20	.34	.21	.15

Note. Marital Status (married = 1, not married = 0), employment status (employed = 1, not employed = 0), educational level (High School = 0, College = 1), neoadjuvant or adjuvant treatment (neoadjuvant or adjuvant = 1, no neoadjuvant or adjuvant = 0), treatment modality (surgery = 1 versus EBRT = 0; brachytherapy = 1 versus EBRT = 0).

[†] p < .10,

* $p < .05$,
** $p < .01$,
*** $p < .001$.