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Factors associated with poor quality of life among cervical cancer survivors: Implications for clinical care and clinical trials ☆

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HIGHLIGHTS

- Cervical cancer patients report prolonged quality of life (QOL) disruption, and are a vulnerable survivor population.
- Patients reported lower QOL and higher levels of depression and anxiety than general and survivor populations.
- Psychological and physical health factors which contribute to poor long-term QOL were identified for intervention.

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ABSTRACT

Introduction. The purpose of this study is to identify factors that are associated with poor quality of life (QOL) among cervical cancer survivors.

Methods. Patients identified through the California Cancer Registry were recruited to participate in a randomized counseling intervention. Patient-reported outcomes (PROs) were collected at study baseline (9–30 months post-diagnosis) and subsequent to the intervention. Multivariable linear models were used to identify independent factors associated with poor baseline QOL.

Results. Non-Hispanic ($N = 121$) and Hispanic ($N = 83$) women aged 22–73 completed baseline measures. Approximately 50% of participants received radiation therapy with or without chemotherapy. Compared to the US population, cervical cancer patients reported lower QOL and significantly higher levels of depression and anxiety (26% and 28% >1 SD above the general population means, respectively). Among those in the lowest quartile for QOL, 63% had depression levels >1 SD above the mean. In addition, treatment with radiation ± chemotherapy ($p = 0.014$), and self-reported comorbidities predating the cancer diagnosis ($p < 0.001$) were associated with lower QOL. Sociodemographic characteristics explained only a small portion of variance in QOL ($r^2 = 0.23$). Persistent gynecologic problems, low social support, depression, somatization, less adaptive coping, comorbidities, sleep problems and low education were all independently associated with low QOL in multivariate analysis ($r^2 = 0.74$).

Conclusion. We have identified key psychological and physical health factors that contribute significantly to poor quality of life subsequent to definitive cancer treatment. The majority of these factors are amenable to supportive care interventions and should be evaluated at the time of primary treatment.

Introduction

Cervical cancer is the second most common female cancer worldwide [1] and survivors often experience significant quality of life (QOL) disruptions associated with the disease and treatment, many of which persist long into survivorship [2–7]. A recent analysis of health-related quality of life data among U.S. cancer survivors indicates that cancer survivors are more likely to have poor physical and mental

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health-related quality of life (25% and 10%, respectively, >1 SD above the US population mean) compared to adults with no cancer history (10% and 5%, respectively). Cervical cancer survivors, and short-survival cancer survivors, report the worst mental health-related quality of life [8].

Persistent sequelae include pain, bladder and bowel dysfunction [9–12], sexual dysfunction [13–16], lymphedema, and menopausal symptoms [17] as well as reproductive concerns among women of childbearing age [5,18–21]. Adverse psychological consequences are shared with women diagnosed with other gynecologic tumors, and include depression and anxiety [22], sleep disturbance, and concentration difficulties to a greater magnitude than many other cancer patient populations [23–25]. Despite challenges inherent in this cancer survivor population, supportive interventions may assist in significantly improving quality of life, with potential to also improve stress-related biomarkers [26]. This could, in turn, improve disease outcomes [27–29].

Although QOL has traditionally been examined as an outcome, it has also been considered as a predictor of survival [4,16,30]. To that end, QOL and other patient reported outcome (PRO) measures can identify cancer patients most at risk for subsequent health problems. Identification of at-risk survivor populations can guide the allocation of supportive care measures during and after cancer treatment. The purpose of this study is to identify factors associated with compromised quality of life for cervical cancer survivors.

Methods

Cervical cancer patients, identified through the California Cancer Registries (CCR), were recruited and consented to participate in a randomized psychosocial telephone counseling trial from 2008 to 2012. Thirty percent of eligible subjects enrolled in the study. Baseline PRO measures were collected subsequent to informed consent and analyzed for associations with patient characteristics.

Eligibility criteria

Participants were eligible for this study if they had been diagnosed with Stage I, II, III or IVa disease, had completed definitive cancer treatment at least two months earlier and were free of disease, and were diagnosed not more than 30 months prior to enrollment. All patients provided informed consent consistent with federal, state and local requirements prior to enrolling in the study. Baseline questionnaires were completed by patients in English or Spanish prior to randomization to telephone counseling or usual care.

Measures

Quality of life

The FACT-Cx (Functional Assessment of Cancer Therapy-Cervical) is a multidimensional, combined generic and disease-specific QOL questionnaire for cervical cancer patients. Scores range from 0 to 168 with higher scores indicating better QOL. The FACT-G (general) questionnaire (version 4) is a 27-item self-report measure that consists of four subscales (physical well-being, social well-being, emotional well-being and functional well-being) [31,32], and an additional concerns subscale, which consists of fifteen items reflecting issues specific to cervical cancer. Scales can be analyzed separately, summed to produce a total FACT-Cx QOL score, or combining the Physical, Functional and Additional Concerns to produce the FACT-Trial Outcome Index (FACT-TOI).

Gynecologic problems

The Gynecologic Problems Checklist (GPC) [2,33,34] identifies the type and magnitude of gynecologic problems using two subscales: gynecologic problems (e.g., pelvic pain, vaginal dryness; Cronbach's alpha = 0.72) and sexual dysfunction (e.g., pain with intercourse, loss of interest in sexual activities; Cronbach's alpha = 0.90). Subscales are summed to yield a total score ranging from 10 to 50 with higher scores reflecting greater severity.

Emotional distress

The Patient-Reported Outcomes Measurement Information System (PROMIS; www.NIHPROMIS.org) short forms were used to measure depression and anxiety. The PROMIS emotional distress short form consists of 15 items; 8 items on depression and 7 items on anxiety. Each item in the PROMIS SF is scored from 1 to 5 points where, 1 = never, 2 = rarely, 3 = sometimes, 4 = often and 5 = always. A high score on these PROMIS short forms connotes more emotional distress (i.e., more depression or anxiety). Standardized T-scores are calculated with mean = 50 and SD = 10. T-scores are normed to the general population so that a score of 50 represents the mean for the US population; a score of 60 denotes a level of depression or anxiety that is one standard deviation above the general population mean.

The Brief Symptom Inventory (BSI-18), also used in this study, is a measure of psychological distress. Each item is rated on a 5-point Likert scale from 0 (not at all) to 4 (always/extremely). Patients are asked to respond to each item in terms of "how they have been feeling during the past 7 days." The BSI-18 includes subscales measuring depression, anxiety and somatization, as well as an overall total score. Standardized scores are normed to the general population, with a mean of 50 and SD = 10 [2,35].

Social support

The MOS Social Support measure is a 19-item, multidimensional, self-administered survey of social support developed for the Medical Outcomes Survey of patients with chronic conditions [36]. Items reflect

Table 1
Descriptive characteristics of the study population.

	Mean	SD
Age at diagnosis	43.1 (range, 22–73)	9.6
Age at study	44.7	9.6
Time from diagnosis to T1 (mo)	19.2	5.4
	N	***%***
Race/Ethnicity		
Caucasian/Non-Hispanic	105	51.5
African-American	4	2.0
Hispanic	83	40.7
Asian/Pacific Islander	11	5.4
Native American	1	0.5
Marital Status		
Single	31	15.3
Married	129	63.6
Separated/Widowed/Divorced	43	21.1
Income		
<$15,000	51	29.3
$15,000–$35,000	32	18.4
$35,000–$55,000	25	14.4
≥$55,000	66	37.9
Education		
<High School	43	21.3
High school graduate	40	19.8
Some college	56	27.7
College graduate	33	16.3
Graduate/professional	30	14.9
Stage		
Stage 1	147	73.1
Stage II	28	13.9
Stage III–IVA	26	12.9
Treatment		
Surgery only	100	49.0
Radiation only	15	7.4
Radiation ± chemo	89	43.6
Comorbidities prior to diagnosis		
None	81	40.1
1	27	13.4
2	30	14.9
3+	64	31.7

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Table 2
Distributions of psychological measures.

	Raw scores				Standard scores			
	N	Mean	SD	Range	*N*	Mean	SD	Range
FACT-Cx	203	124.7	24.3	54–165				
FACT-Trial Outcome Index	200	86.8	17.4	36–114				
FACT-G	203	80.7	18.4	27–108	203	59.8	10.3	41–100
FACT-PWB	201	22.7	5.5	3–18	201	74.7	17.8	24–100
FACT-SWB	203	19.9	6.0	3–28	203	62.1	17.3	25–100
FACT-EWB	204	17.7	4.7	2–24	204	65.1	17.8	18–100
FACT-FWB	204	20.2	6.4	1–28	204	66.7	18.4	9–100
FACT-Additional Concerns (Cx)	203	44.0	8.3	21–60				
Emotional Distress-Depression TS	203	17.1	7.5	8–40	203	53.3	9.8	37–81
Emotional Distress-Anxiety TS	203	16.1	7.4	7–35	203	53.8	11.4	36–83
Perceived Stress Scale (PSS)	189	17.9	7.5	0–34				
Brief Symptom Inventory (BSI)	204	12.5	11.5	0–57	204	51.7	11.8	31–80
Social Support (SS-MOS)	203	3.8	0.9	1.3–5	203	71.1	22.9	8–100
Adaptive Coping (Brief COPE)	202	41.5	10.3	16–64				
Maladaptive Coping (Brief COPE)	202	14.1	4.2	8–26				
Gynecologic Problems Checklist (GPC)	194	20.8	8.2	10–42				
MOS Sleep Problems Index	203	37.5	21.5	0–88				

how often a particular source of support is available and are scored from 1 (none of the time) to 5 (all of the time). The scale has been shown to have good construct validity, high reliability (alpha > 0.91 for all subscales) and to be stable over time.

Coping

The Brief COPE is a 28-item questionnaire adapted from the full COPE [37] and is designed to measure ways in which people respond to stress. Factor structure is similar to the full COPE. Items ask about coping strategies used over the past month and are rated on a 4-point Likert scale ranging from 1 = "I didn't do this at all" to 4 = "I did this a lot". In this study, we created subscales, which distinguish between adaptive (Cronbach's alpha = 0.87) and maladaptive (Cronbach's alpha = 0.68) coping.

Perceived stress

The 10-item Perceived Stress Scale assesses perceptions of stress over the past month [38]. Items reflect how frequently the patient experienced a specific feeling/state, and are rated on a 5-point Likert scale (0 = never to 4 = very often). The PSS has good construct and convergent validity as evidenced by correlations with other measures of stress and self-reported health. Possible scores range from 0 to 40 with higher scores reflecting greater distress [39].

Medical outcomes sleep scale

The 12-item self-reported sleep measure developed for the Medical Outcomes Study (MOS) provides assessment of various dimensions of sleep including initiation, maintenance, respiratory problems, quantity, perceived adequacy and somnolence [40]. A 9-item sleep problems index ranges from 0 (no problems) to 100 (severe sleep problems). Internal consistency reliability estimates for the MOS sleep scales were ≥0.63. The MOS sleep measure has been validated in the US general population and patients with neuropathic pain and found to be responsive to change over time in clinical trials [40].

Sociodemographic and disease characteristics

Age, ethnicity, marital status, education, and income data were collected by questionnaire at baseline. Comorbidities prior to cancer diagnosis were self-reported by patients using a 29-item checklist. Disease stage was derived from the CCR database from which patients were recruited. Treatment data were provided by patients at baseline, and validated by comparison to the CCR data.

Statistical analyses

Summary scores were calculated for all outcome measures with some imputation for missing values. Only 1.7% of the total number of

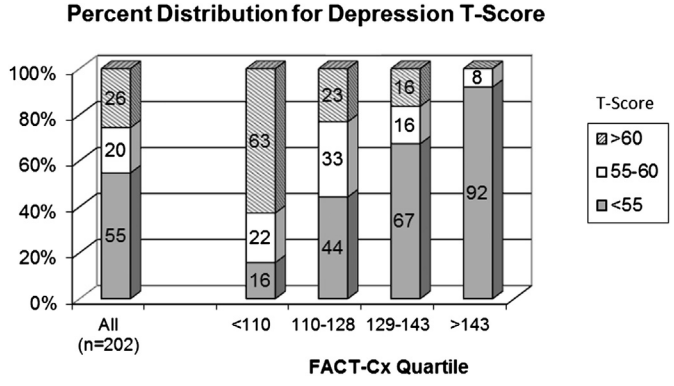

Fig. 1. Percent distribution of emotional distress-depression T-scores (PROMIS) by FACT-Cx quartiles. Fact-Cx quartiles from lowest (1) to highest (4) include scores <110, 110–128, 129–143 and >143. Overall, 26% of cervical cancer survivors report depression T-scores of >60 (>1 SD above the general population mean). Among those with the lowest QOL (FACT-Cx < 110), 63% report depression T-scores of >60 and 84% report depression T-scores of >55 (>0.5 SD above the mean). (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

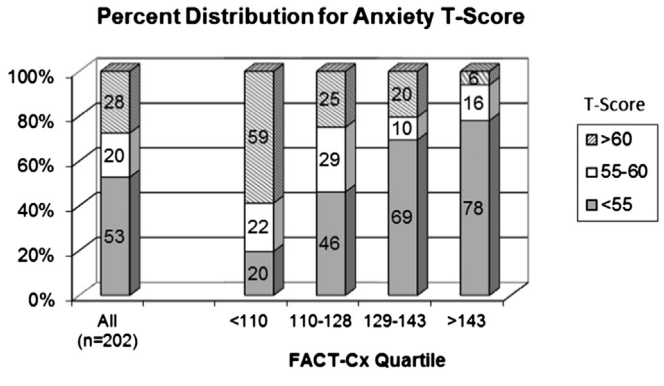

Fig. 2. Percent distribution of emotional distress-anxiety T-scores (PROMIS) by FACT-Cx quartiles. Fact-Cx quartiles from lowest (1) to highest (4) include scores <110, 110–128, 129–143 and >143. Overall, 28% of cervical cancer survivors reported anxiety T-scores of >60 (>1 SD above the general population mean). Among women with low QOL (Fact-Cx < 110), 80% reported anxiety levels of >0.5 SD above the general population mean and 59% reported anxiety of >1 SD above the general population mean. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

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Table 3
Adjusted mean scores for psychosocial measures by clinical and sociodemographic characteristics.*

	FACT-Cx					FACT-TOI					Depression T-Score					Anxiety T-Score				
	N	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size
Ethnicity																				
Hispanic	79	129.7	3.2	0.236	0.18	78	91.0	2.3	0.085	0.26	78	51.7	1.4	0.410	0.14	79	53.0	1.6	0.868	0.03
Non-Hispanic	119	125.2	2.2			118	86.4	1.6			119	53.1	1.0			119	52.7	1.1		
Age																				
≤40	76	127.0	2.9	0.553	0.12	75	88.0	2.1	0.416	0.17	75	53.3	1.3	0.497	0.09	76	53.9	1.5	0.625	0.11
41–50	70	125.3	2.8			69	87.1	2.0			70	51.3	1.2			70	52.0	1.4		
>50	52	129.9	3.5			52	90.9	2.4			52	52.5	1.5			52	52.7	1.8		
Education																				
≤ High school	80	123.7	2.8	0.134	0.35	79	86.0	2.0	0.063	0.38	80	53.0	1.3	0.835	0.11	80	54.2	1.4	0.428	0.10
Some College	55	126.4	3.3			55	87.3	2.3			55	52.1	1.4			55	51.4	1.7		
Col Grad/Prof	63	132.1	3.3			62	92.6	2.3			63	52.0	1.5			63	53.0	1.7		
Stage																				
I	145	122.8	2.0	0.036	0.38	144	86.1	1.4	0.105	0.29	146	53.9	0.9	0.126	0.30	146	54.6	1.0	0.125	0.30
II–IVA	53	132.1	3.7			52	91.2	2.6			52	50.9	1.6			52	51.1	1.9		
Treatment																				
Radiation ± chemo	99	122.4	2.3	0.014	0.41	98	84.8	1.6	0.006	0.45	98	54.1	1.0	0.051	0.35	98	54.6	1.2	0.079	0.31
Surgery only	99	132.4	3.3			98	92.6	2.3			100	50.6	1.4			100	51.0	1.7		
Comorbidities																				
0	78	138.4	2.7	<0.001	0.93	77	96.5	1.9	<0.001	0.95	78	50.4	1.2	0.002	0.57	78	50.4	1.4	0.004	0.56
1–2	57	128.1	3.2			57	89.4	2.3			57	50.7	1.4			57	51.4	1.6		
3+	63	115.7	3.1			62	80.0	2.2			62	56.0	1.4			62	56.8	1.6		
	N	Mean	SD	R^2		*N*	Mean	SD	R^2		*N*	Mean	SD	R^2		*N*	Mean	SD	R^2	
All	198	125.1	24.1	0.228		196	87.2	17.1	0.246		197	53.2	9.8	0.108		197	53.7	11.4	0.109	

	Perceived Stress					BSI-GSI T-Score					Social Support-Standard Score					GPC-Total				
	N	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size
Ethnicity																				
Hispanic	76	14.4	1.0	0.002	0.50	79	48.7	1.6	0.110	0.25	78	76.2	3.2	0.220	0.20	71	20.0	1.2	0.756	0.05
Non-Hispanic	107	18.2	0.7			119	51.7	1.1			119	71.5	2.2			117	20.4	0.8		
Age																				
≤40	67	17.4	1.0	0.356	0.23	76	49.6	1.5	0.508	0.01	75	76.6	2.9	0.358	0.12	73	19.7	1.1	0.151	0.06
41–50	65	15.8	0.9			70	51.5	1.4			70	71.2	2.8			67	21.8	1.0		
>50	51	15.6	1.1			52	49.5	1.8			52	73.8	3.5			48	19.1	1.3		
Education																				
≤ High school	76	17.3	0.9	0.469	0.20	80	51.2	1.4	0.602	0.18	79	71.9	2.9	0.724	0.15	73	19.7	1.1	0.578	0.01
Some College	47	15.9	1.1			55	50.4	1.7			55	74.5	3.3			54	21.1	1.2		
Col Grad/Prof	60	15.7	1.0			63	49.0	1.7			63	75.2	3.3			61	19.8	1.2		
Stage																				
I	134	18.7	0.6	0.001	0.65	145	52.5	1.0	0.041	0.39	144	68.1	2.0	0.009	0.51	139	20.8	0.7	0.441	0.15
II–IVA	49	13.8	1.2			53	47.9	1.9			53	79.6	3.7			49	19.6	1.4		
Treatment																				
Radiation ± chemo	91	17.7	0.7	0.031	0.38	99	51.6	1.2	0.182	0.23	99	71.2	2.3	0.189	0.23	94	22.7	0.8	0.001	0.60
Surgery only	92	14.9	1.1			99	48.8	1.7			98	76.5	3.3			94	17.7	1.2		
Comorbidities																				
0	72	13.4	0.9	<0.001	0.87	78	46.1	1.4	<0.001	0.81	78	81.0	2.7	0.002	0.59	74	19.1	1.0	0.314	0.26
1–2	53	15.5	1.0			57	48.9	1.6			57	73.0	3.2			56	20.2	1.2		
3+	58	19.9	1.0			63	55.6	1.6			62	67.5	3.1			58	21.2	1.2		
	N	Mean	SD	R^2		*N*	Mean	SD	R^2		*N*	Mean	SD	R^2		*N*	Mean	SD	R^2	
All	183	17.7	7.5	0.249		198	51.4	11.7	0.164		197	71.2	22.7	0.128		188	20.5	8.0	0.119	

	Adaptive Coping					Maladaptive Coping					Sleep Problems (MOS)				
	N	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size
Ethnicity															
Hispanic	78	46.2	1.4	<0.001	0.64	78	14.4	0.6	0.247	0.19	78	35.3	2.6	0.444	0.12
Non-Hispanic	118	39.7	1.0			118	13.6	0.4			119	38.0	2.0		
Age															
≤40	75	40.2	1.3	0.026	0.44	75	13.2	0.5	0.100	0.40	75	35.3	2.5	0.668	0.08
41–50	69	44.1	1.3			69	13.9	0.5			70	38.5	2.5		
>50	52	44.7	1.6			52	14.9	0.6			52	37.1	3.0		
Education															
≤ High school	79	42.5	1.3	0.788	0.12	79	14.8	0.5	0.182	0.22	79	40.1	2.6	0.297	0.28
Some College	55	42.7	1.5			55	13.3	0.6			55	35.7	2.8		
Col Grad/Prof	62	43.7	1.5			62	13.9	0.6			63	34.0	2.7		
Stage															
I	143	41.4	0.9	0.105	0.31	143	14.2	0.4	0.618	0.10	144	41.2	1.8	<0.001	0.73
II–IVA	53	44.6	1.7			53	13.8	0.7			53	25.4	3.3		
Treatment															
Radiation ± chemo	97	43.5	1.0	0.514	0.11	99	14.9	0.4	0.013	0.44	99	40.1	2.4	0.095	0.29
Surgery only	99	42.4	1.5			97	13.1	0.6			98	33.8	2.4		

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Table 3 *(continued)*

	Adaptive Coping					Maladaptive Coping					Sleep Problems (MOS)				
	N	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size	*N*	Mean	SE	*p*-value	Effect size
Comorbidities															
0	78	43.8	1.2	0.063	0.08	78	14.0	0.5	0.432	0.12	77	33.7	2.4	0.124	0.34
1–2	55	40.5	1.5			56	13.5	0.6			57	36.8	2.7		
3+	62	44.6	1.4			62	14.5	0.6			63	41.1	2.6		
	N	Mean	SD	R^2		*N*	Mean	SD	R^2		*N*	Mean	SD	R^2	
All	196	41.4	10.4	0.164		196	14.0	4.2	0.137		197	36.9	21.4	0.120	

* Controlling for age, ethnicity, education, stage, treatment and comorbidities.

items was missing and deemed to be missing at random. Missing items were handled according to the administration/scoring procedures in the FACT manual, prorating subscales scores under the constraints that >50% of subscale items and >80% of all items must be completed in order to create subdomain and total scores (www.facit.org). Among subjects who had completed at least 80% of all items but had some missing data, the average number of missing items ranged from 1.2 to 2.4 items for the various scales reported.

Descriptive statistics were computed for all patient characteristics and outcome measures (means and SDs for continuous variables, frequencies and percentages for categorical variables). Associations between patient characteristics and outcome measures were first tested using bivariate *t*-tests and analysis of variance. Sociodemographic and disease characteristics that were significantly associated with at least one of the outcome measures ($p < 0.05$) were included in multivariable analyses. Marital status and time from diagnosis to assessment were not significantly associated with any outcome measure and were therefore not included. Income was correlated with education ($r = 0.32$) and was missing for 15% of subjects, thus was not included in multivariate analyses. Adjusted associations between PRO measures and sociodemographic, tumor and treatment variables were tested using multivariable linear models (SYSTAT version 13.0). Effect sizes for PROs were calculated as the difference between subgroup means divided by the SD for the pooled group. Effects in the range of 0.33 to 0.5 have been considered to be a minimal clinically important difference [41,42]. Stepwise linear models with backward elimination and $p = 0.15$ to remove variables were used to identify independent factors associated with QOL. Only 15 patients were treated with radiation alone, thus analyses examined the effects of radiation ± chemotherapy compared to surgery only. Detailed stage information was not available for most patients. Because 73% of women had stage I disease and one-third of these were treated with radiation therapy, stage of disease per se was not informative for multivariate analyses, and instead cancer treatment differences were examined by surgery-only versus radiation ± chemotherapy. Variables entered in the stepwise model included sociodemographics (age, ethnicity and education), treatment, depression, anxiety, somatization, social support, gynecologic problems, coping and sleep disturbance.

Results

Sociodemographic and disease characteristics

Between October 2008 and May 2012, 204 patients were enrolled into the study and completed the baseline assessments, Sociodemographic and disease characteristics are summarized in Table 1. Forty-one percent were Hispanic and 52% were non-Hispanic White. The mean age at study entry was 43.1 years (range, 22–73) and participants were, on average, 19 months past diagnosis (range, 9–30 months) before enrolling in the study. Most participants (73%) had stage I disease and all had completed treatment prior to participation. Forty-nine percent ($n = 100$) were treated with surgery only while 51% ($n = 104$) received radiation with or without chemotherapy. Compared to subjects who declined to participate, those who enrolled were significantly more likely to have early stage disease (73% vs. 61%), be of non-Hispanic white ethnicity (52% vs. 38%), and have a younger age at diagnosis (43 vs. 50 years). However, enrolled subjects included a representative proportion of Hispanics (41% compared to 40% among refusers) and did not differ significantly with respect to treatment.

Quality of life and associations with other PRO measures

Means and standard deviations for all PROs are presented in Table 2. Figs. 1 and 2 illustrate that PROMIS T-scores for depression and anxiety were >55 (0.5 SD above the mean) in 45% and 47% of patients, respectively, while 26% and 28% of patients had T-scores of >60, reflecting clinically significant emotional distress. Among women in the lowest QOL quartile (FACT-Cx < 110), depression and anxiety T-scores of >60 were reported by 63% and 59%, respectively (Figs. 1 and 2). In Table 3, we report both statistical significance and effect size in terms of number of standard deviations to identify characteristics that contribute to clinically important differences in QOL and other PROs.

Quality of life, PROs and associations with cancer treatment

There were notable cancer treatment-associated differences in QOL and PROs (Table 3). Patients who received radiation with or without chemotherapy reported significantly worse QOL (FACT-Cx, $p = 0.014$; FACT-TOI, $p = 0.006$) after adjusting for other covariates, compared to the surgery-only patients. Effect sizes were >0.4 SD in magnitude. Patients receiving radiation with or without chemotherapy also reported higher perceived stress (PSS, $p = 0.031$, effect size = 0.38 SD) depression (ED-Dep TS, $p = 0.051$, effect size = 0.35 SD) and anxiety (ED-Anx TS, $p = 0.079$, effect size = 0.31 SD). Gynecologic problems were also significantly more frequent in those who received radiation (GPC, $p = 0.001$, effect size = 0.60 SD) and maladaptive coping was higher ($p = 0.013$, effect size = 0.44 SD) compared to patients who had surgery only.

Quality of life, PROs and associations with comorbidities

Forty percent of patients reported no major illness prior to their cancer diagnosis, while 32% reported 3 or more comorbid conditions that predated the cancer diagnosis. Among these co-morbid conditions, in greatest frequency, 21% reported back pain, 18% reported depression, 16% reported migraine headaches and 15% reported anxiety. Prior comorbid conditions were associated with significantly lower QOL ($p < 0.001$ for both FACT-Cx and FACT-TOI), significantly higher perceived stress, depression and anxiety ($p < 0.01$ for each), and significantly lower social support ($p = 0.002$). Effect sizes were large, ranging from 0.56 to 0.95. Reported comorbid conditions were not associated with gynecologic problems or coping.

Multivariable prediction of quality of life

Sociodemographic and patient characteristics alone explained only a small proportion of the variance in QOL with *R*-squared = 0.23. When sociodemographics, patient characteristics and PROs were included in a multivariable linear model to explain overall QOL (Table 4); higher

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Table 4
Factors Associated with Baseline Quality of Life (FACT-Cx) in stepwise multivariate linear regression. Dependent variable = FACT-Cx, independent variables included in stepwise model: BSI-Depression T-Score, BSI-Anxiety T-Score, BSI-Somatization T-Score, Emotional Distress-Depression T-Score, Emotional Distress-Anxiety T-Score, Social Support (MOS) Standard Score, Gynecologic Problems Checklist, Perceived Stress, Adaptive coping, Maladaptive coping, age, ethnicity, education, treatment, and comorbidity. Multiple $r = 0.86$. Adjusted multiple $r^2 = 0.74$.

Independent Variable	Coefficient	Standard Error	Standard Coefficient	*p*-value
Gynecologic Problems Checklist	−0.834	0.127	−0.281	<0.001
Social Support Standard Score	0.277	0.049	0.264	<0.001
ED-Depression T-score	−0.561	0.121	−0.226	<0.001
BSI-Somatization T-score	−0.507	0.131	−0.210	<0.001
Adaptive Coping	0.365	0.094	0.153	<0.001
Comorbidity (<3 vs. 3+)	−5.784	2.180	0.113	0.009
Sleep (MOS)	−0.126	0.059	−0.112	0.035
Education (≤HS vs. other)	3.882	1.931	0.080	0.046

Age, ethnicity, treatment, and perceived stress were not significant in the multivariate model ($p > 0.3$ for each). Anxiety (BSI and ED) was excluded from the model because of low tolerance (<0.4).

levels of depression, somatization, gynecologic problems, sleep disturbance, comorbidities prior to cancer diagnosis, and lower levels of adaptive coping, social support and education were independently associated with lower QOL ($p < 0.04$ for each). Standard coefficients indicate that gynecologic problems, social support, depression, and somatization (BSI) were most strongly associated with poor QOL while coping, comorbidity, sleep disturbance and education explained smaller amounts of the variance. The adjusted squared multiple correlation was 0.74. Anxiety was not included in the model because of low tolerance and multi-collinearity. Because treatment with radiation with or without chemotherapy is associated with poor outcome for nearly every PRO, treatment was not independently associated with QOL in the multivariate model after inclusion of other PROs. Age, ethnicity and perceived stress were not significantly associated with QOL after adjusting for other variables.

Discussion

The purpose of this study was to identify factors associated with poor quality of life among cervical cancer survivors, in order to identify emotional, physical or social domains that could be prioritized for screening and supportive care. To our knowledge, this is the first study to identify the substantial symptoms of depression and anxiety in this survivor population, which exist long after cancer treatment has concluded. This magnitude of distress clearly influences and disrupts overall quality of life. For example, among women in the lowest quartile for QOL (as measured by the FACT-Cx < 110), 63% reported depression and 59% reported anxiety on the PROMIS measures, with scores that exceeded the clinically meaningful threshold [43]. Notably, these scores represent a tentative threshold for moderate depression, which PROMIS has set on the Depression measure of 60, or 1 SD above the population mean [43,44]. Our results on emotional distress correspond to a similar population-based study from the Netherlands, which also reported that the cervical cancer survivor population had mental health scores worse than the reference population [6].

Patients reporting the worst QOL also reported more gynecologic problems, and less social support. The direct and buffering effects of social support among gynecologic cancer survivors has been previously illustrated [45], and may lend further insight to inform supportive care interventions for this population. Persistent gynecologic problems, however, can be linked to cancer treatment. Not surprisingly, gynecological problems were significantly worse in patients treated with radiation with or without chemotherapy, compared to those treated with surgery only, with a moderate-to-large effect size, which is both statistically and clinically significant. Treatment with radiation with or without chemotherapy also contributed to significantly poorer QOL, higher perceived stress and greater depression, with modest-to-moderate effect sizes. Use of a clinic-based gynecologic problems checklist could potentially serve as a physician–patient communication tool while simultaneously monitoring outcomes. Although it is known that radiated patients generally have poorer QOL, we did not expect that they also suffered more stress and depression. Therefore, one could anticipate that patients receiving radiation therapy could be considered an especially vulnerable subpopulation within a population that is already at greater risk of poor QOL during survivorship.

Furthermore, patients with three or more comorbidities prior to cancer diagnosis also reported significantly worse QOL, higher perceived stress, more depression and anxiety, and lower social support. In identifying subpopulations that are likely to benefit from supportive care interventions, it appears that a brief screening of type and number of premorbid medical problems, including mood disorders, could target those at greatest need for more immediate care and attention, as well as future cancer control studies. Early screening of distress, consistent with NCCN guidelines [46], QOL and premorbid conditions could assist in patient comfort, and perhaps compliance, during and subsequent to treatment. Although our earlier pilot of a psychosocial telephone counseling intervention did promote quality of life improvement [26], we did not screen for distress. Therefore, further study of supportive care interventions to improve distress and decrease gynecologic problems in this vulnerable population appear warranted, particularly for women whose cancer treatment extends beyond surgery.

Conflict of interest statement

The authors have no conflicts to report.

References

[1] Jemal A, Simard EP, Dorell C, et al. Annual report to the nation on the status of cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV) associated cancers and HPV vaccination coverage levels. JNCI J Natl Cancer Inst Feb 2013;105(3):175–201.
[2] Wenzel L, DeAlba I, Habbal R, et al. Quality of life in long-term cervical cancer survivors. Gynecol Oncol May 2005;97(2):310–7.
[3] Ashing-Giwa KT, Tejero JS, Kim J, et al. Cervical cancer survivorship in a population based sample. Gynecol Oncol Feb 2009;112(2):358–64.
[4] Ashing-Giwa KT, Lim JW, Tang J. Surviving cervical cancer: does health-related quality of life influence survival? Gynecol Oncol Jul 2010;118(1):35–42.
[5] Bodurka DC, von Gruenigen VE. Women's cancer survivorship: time to gear up! Gynecol Oncol Mar 2012;124(3):377–8.
[6] Korfage IJ, Essink-Bot ML, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-related quality of life in cervical cancer survivors: a population-based survey. Int J Radiat Oncol Apr 1 2009;73(5):1501–9.
[7] Distefano M, Riccardi S, Capelli G, et al. Quality of life and psychological distress in locally advanced cervical cancer patients administered pre-operative chemoradiotherapy. Gynecol Oncol Oct 2008;111(1):144–50.
[8] Weaver KE, Forsythe LP, Reeve BB, et al. Mental and physical health-related quality of life among US cancer survivors: population estimates from the 2010 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev Nov 2012;21(11):2108–17.
[9] Lutgendorf SK, Anderson B, Rothrock N, Buller RE, Sood AK, Sorosky JI. Quality of life and mood in women receiving extensive chemotherapy for gynecologic cancer. Cancer Sep 15 2000;89(6):1402–11.
[10] Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Lymphedema and bladder-emptying difficulties after radical hysterectomy for early cervical cancer and among population controls. Int J Gynecol Cancer May-Jun 2006;16(3):1130–9.
[11] Skjeldestad FE, Rannestad T. Urinary incontinence and quality of life in long-term gynecological cancer survivors: a population-based cross-sectional study. Acta Obstet Gynecol Scand 2009;88(2):192–9.
[12] Grover S, Hill-Kayser CE, Vachani C, et al. Patient reported late effects of gynecological cancer treatment. Gynecol Oncol Mar 2012;124(3):399–403.
[13] Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. Gynecol Oncol Mar 2012;124(3):477–89.
[14] Bodurka DC, Sun CC. Sexual function after gynecologic cancer. Obstet Gyn Clin N Am Dec 2006;33(4):621–30.
[15] Lindau ST, Gavrilova N, Anderson D. Sexual morbidity in very long term survivors of vaginal and cervical cancer: a comparison to national norms. Gynecol Oncol Aug 2007;106(2):413–8.
[16] Baze C, Monk BJ, Herzog TJ. The impact of cervical cancer on quality of life: a personal account. Gynecol Oncol May 2008;109(2):S12–4.
[17] Ferrandina G, Mantegna G, Petrillo M, et al. Quality of life and emotional distress in early stage and locally advanced cervical cancer patients: a prospective, longitudinal study. Gynecol Oncol Mar 2012;124(3):389–94.

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[18] Sun C, Jhingran A, Gallegos J, Bodurka D, Frumovitz M, Ramondetta L. Longitudinal quality of life in medically underserved women with locally advanced cervical cancer. Gynecol Oncol Mar 2012;125:S50-S50.
[19] Bodurka D, Sun C, Jhingran A, et al. A longitudinal evaluation of sexual functioning and quality of life in cervical cancer survivors. Gynecol Oncol Mar 2011;121(1):S81–2.
[20] Wenzel L, Dogan-Ates A, Habbal R, et al. Defining and measuring reproductive concerns of female cancer survivors. J Natl Cancer Inst Monogr 2005;34:94–8.
[21] Frumovitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol Oct 20 2005;23(30):7428–36.
[22] Mantegna G, Petrillo M, Fuoco G, et al. Long-term prospective longitudinal evaluation of emotional distress and quality of life in cervical cancer patients who remained disease-free 2-years from diagnosis. BMC Cancer Mar 18 2013;13.
[23] Bradley S, Rose S, Lutgendorf S, Costanzo E, Anderson B. Quality of life and mental health in cervical and endometrial cancer survivors. Gynecologic Oncology Mar 2006;100(3):479–86.
[24] Herzog TJ, Wright JD. The impact of cervical cancer on quality of life—the components and means for management. Gynecol Oncol Dec 2007;107(3):572–7.
[25] Ashing-Giwa KT, Lim JW, Gonzalez P. Exploring the relationship between physical well-being and healthy lifestyle changes among European- and Latina-American breast and cervical cancer survivors. Psycho-Oncology Nov 2010;19(11):1161–70.
[26] Nelson EL, Wenzel LB, Osann K, et al. Stress, immunity, and cervical cancer: Biobehavioral outcomes of a Randomized clinical trail. Clin Cancer Res Apr 1 2008;14(7):2111–8.
[27] Antoni MH. Psychosocial intervention effects on adaptation, disease course and biobehavioral processes in cancer. Brain Behav Immun Mar 15 2013;30:S88–98.
[28] Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. Brain Behav Immun Mar 15 2013;30:S41–7.
[29] Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol Aug 2008;5(8):466–75.
[30] Chase DM, Huang HQ, Wenzel L, et al. Quality of life and survival in advanced cervical cancer: a Gynecologic Oncology Group study. Gynecol Oncol May 2012;125(2):315–9.
[31] Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol Off J Am Soc Clin Oncol Mar 1993;11(3):570–9.
[32] Tewari KS, Sill MW, Long 3rd HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med Feb 20 2014;370(8):734–43.
[33] Wenzel L, Osann K, Hseih S, Chantana N, Sappington S, Marquez D, Nelson E. Quality of life outcomes of a randomized counseling trial for cervical cancer survivors. Qual Life Res Oct 2012;21(1–132) 15 [Abstract 108.3].
[34] Wenzel L. Late Effects and Quality of Life following Aggressive Management. Chicago IL: American Brachytherapy Society GYN School; July, 2014.
[35] Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med Aug 1983;13(3):595–605.
[36] Sherbourne CD, Stewart AL. The MOS Social Support Survey. Soc Sci Med 1991;32(6):705–14.
[37] Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4(1):92–100.
[38] Cohen S, Williamson GM. Perceived stress in a probability sample of the United-States. Clar Symp; 1988. p. 31–67.
[39] Cohen S, Rabin BS. Psychologic stress, immunity, and cancer. J Natl Cancer Inst Jan 7 1998;90(1):3–4.
[40] Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Med Jan 2005;6(1):41–4.
[41] Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six patient-reported outcomes. Measurement information system-cancer scales in advanced-stage cancer patients. J Clin Epidemiol May 2011;64(5):507–16.
[42] Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). J Clin Epidemiol Nov 2010;63(11):1195–204.
[43] Choi SW, Schalet B, Cook KF, Cella D. Establishing a common metric for depressive symptoms: linking the BDI-II, CES-D, and PHQ-9 to PROMIS depression. Psychol Assess Jun 2014;26(2):513–27.
[44] Cella D, Lai J, Garcia SF, et al. The Patient Reported Outcomes Measurement Information System-Cancer (PROMIS-Ca): cancer-specific application of a generic fatigue measure. J Clin Oncol May 20 2008;26(15).
[45] Khan NF, Carpenter L, Watson E, Rose PW. Cancer screening and preventative care among long-term cancer survivors in the United Kingdom. Br J Cancer Mar 30 2010;102(7):1085–90.
[46] National Comprehensive Cancer Network I. NCCN Guidelines™ Version 1.2011 Panel Members Distress Management. NCCN.Org; 2011.

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