Scientific Article

Patient-reported distress and survival among patients receiving definitive radiation therapy

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Abstract

Objective: Patient-reported distress (PRD) has not been well assessed in association with survival after radiation therapy (RT). The aims of this study were to evaluate the association between PRD level and survival after definitive RT and to identify the main causes of distress in definitive RT patients.

Methods and materials: A total of 678 consecutive patients receiving definitive RT at our institution from April 2012 through May 2015 were included. All patients answered a PRD questionnaire that contained 30 items related to possible causes of distress, which could be rated from 1 (no distress) to 5 (high distress). Additionally, patients were asked to rate their overall distress level from 0 (no distress) to 10 (extreme distress). This overall distress level was our primary

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patient-reported distress measure and was examined as a continuous variable and as a categorical variable with 3 PRD levels (low, 0-3 [n = 295]; moderate, 4-6 [n = 222]; and high, 7-10 [n = 161]).

Results: As a continuous variable in multivariable Cox regression analysis, a higher overall PRD level was associated with poorer survival after RT (hazard ratio [HR], 1.39; *P* = .004). As a categorical variable, compared with patients with low distress, survival was poorer for patients with moderate distress (HR, 1.62; *P* = .038) or high distress (HR, 1.49; *P* = .12), but the latter difference was not significant. When the moderate and high distress levels were combined, survival was significantly poorer compared with the low distress level (HR, 1.57; *P* = .034). The top 5 specific causes of distress that patients mentioned were "How I feel during treatment," "Fatigue," "Out-of-pocket medical costs," "Pain that affects my daily functioning," and "Sleep difficulties."

Conclusions: PRD before or during RT is a prognostic factor associated with decreased survival. Distress screening guidelines and interventions should be implemented for patients receiving definitive RT.

Introduction

Patient-reported distress (PRD) among patients receiving radiation therapy (RT) has not been well characterized. The Institute of Medicine (IOM) and the National Comprehensive Cancer Network (NCCN) consider identifying and addressing psychosocial needs of cancer patients an increasingly important part of the standard of care in oncology,[1,2] and the Commission on Cancer considers it an accreditation standard.[3] The NCCN uses the term *distress* to describe psychosocial concerns. Distress associated with cancer is defined as an unpleasant emotional experience that interferes with the coping abilities of cancer patients. It can be psychologic (cognitive, behavioral, or emotional), spiritual, or social.[4]

Distress is not always recognized. In a study of 143 physicians who provided cancer care and established the psychologic status of 2297 patients at 34 cancer centers, the physicians' mean (standard deviation [SD]) sensitivity for identifying psychologic comorbidity was 29% (25%), and mean (SD) specificity was 85% (17%); 35% (14%) were misclassified with the wrong assessment.[5] At our center, we have successfully implemented a program of standardized screening for distress. The IOM recommends caring for the whole person, including the patient's physical and psychologic well-being. Identifying PRD and decreasing it when possible can improve the patient's quality of life (QOL)[6] and is consistent with the NCCN and IOM guidelines.

The primary objective of this retrospective study was to assess the correlation of PRD to patients' survival after definitive RT. The secondary objective was to identify the main causes of distress among these patients. According to the concept that overall well-being of patients depends on both physical health and psychologic health, our hypothesis was that among oncology patients receiving definitive RT, the patients with higher levels of psychosocial distress have poorer survival after RT.

Methods and materials

Study patients and data collection

A total of 678 consecutive patients who received definitive RT at our institution from April 2012 through May 2015 were included in this retrospective study. We included patients who had filled out a PRD questionnaire within 90 days before the start of RT and were at least 18 years old. Of the 678 patients, 637 (94.0%) completed the PRD questionnaire between 0 and 30 days before the start of RT, 24 (3.5%) completed the questionnaire between 31 and 60 days before the start of RT, and 17 (2.5%) completed the questionnaire between 61 and 90 days before the start of RT. We excluded 8 patients who had endocrine cancers because the number of patients was so small. Patients' medical records were retrospectively assessed to extract information on age at RT, sex, primary cancer site and stage, RT dose, metastatic disease at the start of RT, chemotherapy at or before the start of RT, and surgery at or before the start of RT. There were no missing data, with the exception that data on metastatic disease at the start of RT were unavailable for 1 patient, and cancer stage was unavailable for a relatively large number of patients (167; 25%). The primary outcome measure of the study was overall survival after the start of RT.

PRD evaluation

Patients were asked to complete the PRD questionnaire, which contained 30 items related to possible causes

Distress Screening

Patient Identification

1. Medical treatment can be challenging to all areas of a person's life. Please help us understand how we can best support you by sharing your current concerns.
   I am concerned about...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Housing during treatment	1	2	3	4	5
Transportation to treatment	1	2	3	4	5
Out-of-pocket medical costs	1	2	3	4	5
Finances	1	2	3	4	5
My job	1	2	3	4	5
Managing my medical care	1	2	3	4	5
Completing a medical power of attorney or living will	1	2	3	4	5
A loved one relying on me for their physical care	1	2	3	4	5
How I feel about my appearance related to treatment	1	2	3	4	5
Handling my own bathing, dressing, and daily care	1	2	3	4	5
Fatigue	1	2	3	4	5
Poor concentration or memory	1	2	3	4	5
Pain that affects my daily functioning	1	2	3	4	5
Sexuality	1	2	3	4	5
Irritability	1	2	3	4	5
Sleep difficulties	1	2	3	4	5
My relationship with my spouse/partner	1	2	3	4	5
Family communication about my illness	1	2	3	4	5
Having enough help (emotional and practical)	1	2	3	4	5
Feeling down or depressed	1	2	3	4	5
Loss of interest in my usual activities	1	2	3	4	5
Feeling out of control over important things	1	2	3	4	5
Panic attacks	1	2	3	4	5
Feeling nervous or anxious	1	2	3	4	5
Fear of medical procedures (needles, closed spaces, etc)	1	2	3	4	5
Controlling my anger	1	2	3	4	5
Questions about end of life	1	2	3	4	5
Spirituality	1	2	3	4	5
How I will feel during treatment	1	2	3	4	5
Other (specify) _____	1	2	3	4	5

2. Do you live alone or with others?   Alone_____   With others_____

3. Your diagnosis_____

4. In general, how stressed have you felt in the last month?
   Please look at the thermometer and choose a number from 1 to 10 _____

Extreme Distress 10
9
8
7
6
5
4
3
2
1
No Distress 0
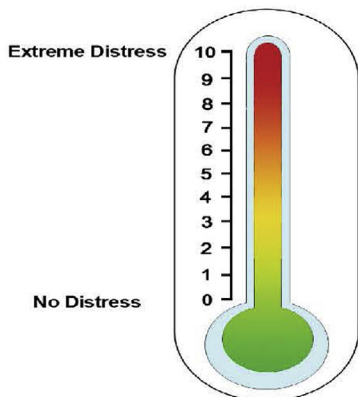
_____   _____   _____
Patient Signature   Date   Time

Official Use Only

Unique

SWCDA

Figure 1   Patient-reported distress form. (data from National Comprehensive Cancer Network[2] and Jacobsen et al[7])

of distress that might affect QOL (Fig 1). Each category was rated from 1 (no distress) to 5 (high distress). The PRD questionnaire was adapted from the Distress Thermometer and Problem List[7] for clinical use at our institution in early 2012. The Distress Thermometer is a validated tool to assess psychosocial distress in cancer patients.[7] Instead of using yes/no answers, our questionnaire used a scale from 1 to 5 for 30 possible causes of distress. It also included a drawing of a distress thermometer, as with the NCCN Distress Thermometer,[2] to measure the patient's overall distress level, with a range from 0 (no distress) to 10 (extreme distress). This 11-point scale provided our primary measure of PRD (called *PRD level*) and was the measure that we used for evaluating the association between patient distress level and survival after RT.

Statistical analysis

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with the number and percentage of patients. Responses to the 30 possible causes of distress in the PRD questionnaire were summarized with the sample mean and with the number and percentage of patients for each response. PRD level was considered as a continuous variable to evaluate a linear trend and as a categorical variable with 3 PRD levels (low, 0-3; moderate, 4-6; and high, 7-10) to evaluate for a potential nonlinear association. Baseline characteristics were compared between patients with low, moderate, or high PRD levels with a Kruskal-Wallis rank sum test or the Fisher exact test. The Kaplan-Meier method was used to estimate survival after the start of RT, where censoring occurred on the date of latest follow-up. Associations between baseline patient characteristics and survival after the start of RT were evaluated with univariable (ie, unadjusted) Cox proportional hazards regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. The association of PRD level (both as a continuous variable and as a categorical variable) with survival after the start of RT was evaluated with univariable and multivariable Cox proportional hazards regression models. Multivariable models were adjusted for all baseline variables that did not have large amounts of missing data, which included age, sex, primary cancer site, RT dose, metastatic disease at the start of RT, chemotherapy at or before the start of RT, and surgery at or before the start of RT. Stage was not adjusted for because of the extent of missing data. HRs and 95% CIs were estimated. *P* values of .05 or less were considered statistically significant. All statistical analyses were performed with SAS software (version 9.2; SAS Institute Inc) and R statistical software (version 2.14.0; R Foundation for Statistical Computing).

Results

Patient characteristics according to PRD level (low, moderate, or high) are compared in Table 1. Differences between the 3 distress level groups were significant for age ($P = .003$), sex ($P = .011$), and primary cancer site ($P < .001$). Specifically, patients with lower reported levels of distress tended to be older and male with a primary cancer site in the genitourinary tract or skin. Differences among the 3 distress level groups were not significant for stage ($P = .19$), dose ($P = .86$), metastatic disease ($P = .14$), chemotherapy ($P = .65$), or surgery ($P = .56$).

Median length of follow-up after the start of definitive RT was 14.1 months (range, 8 days to 39.2 months); 111 patients (16%) died. Kaplan-Meier estimated survival at 6 months, 1 year, and 2 years after the start of RT was 95% (95% CI, 93-97), 87% (95% CI, 85-90), and 78% (95% CI, 74-82), respectively. To better understand how the characteristics shown in Table 1 might act as confounding variables when assessing the relationship between PRD level and survival, we next examined the associations of these characteristics and survival after definitive RT (Table 2). The following associations with survival after RT were significant: age (HR [per 10-year increase], 1.26; $P = .003$); male sex (HR, 1.63; $P = .012$); chemotherapy at or before the start of RT (HR, 2.38; $P < .001$); and surgery at or before the start of RT (HR, 0.57; $P = .004$). Compared with survival for stage 0 or 1 patients, survival was significantly worse for patients with cancer in stage 2 (HR, 3.92; $P = .001$); stage 3 (HR, 5.73; $P < .001$); or stage 4 (HR, 4.37; $P < .001$). Survival after RT was significantly different according to primary cancer site ($P < .001$); compared with the most common site of head and neck, survival was significantly better for patients with breast cancer (HR, 0.06; $P < .001$) and genitourinary cancer (HR, 0.04; $P = .002$). No notable associations with survival after RT were noted for dose ($P = .91$) or metastatic disease ($P = .58$).

Associations between PRD and survival after definitive RT are shown in Table 3. PRD level as a continuous variable showed a significant association with survival in both univariable analysis (HR, 1.34; $P = .007$) and multivariable analysis after adjusting for age, sex, primary cancer site, dose, metastatic disease at the start of RT, chemotherapy at or before the start of RT, and surgery at or before the start of RT (HR, 1.39; $P = .004$). PRD level as a categorical variable in univariable analysis, in comparison to patients with a low-distress level, showed significantly poorer survival after RT for patients with moderate distress (HR, 1.58; $P = .042$) but not for patients in the smaller high-distress group (HR, 1.42; $P = .15$). These results were similar in multivariable analysis (Table 3); however, because the magnitude of difference in survival in comparison to the low-distress

Table 1 Patient characteristics according to distress level at the start of RT[a]

Variable	Low distress, 0-3 (n = 295)[b]	Moderate distress, 4-6 (n = 222)[b]	High distress, 7-10 (n = 161)[b]	P value[c]
Age at start of RT, y	68 (29-97)	66 (27-90)	63 (23-93)	.003
Male	161 (54.6)	98 (44.1)	67 (41.6)	.011
Primary cancer site				<.001
Head and neck	53/147 (36.1)	60/147 (40.8)	34/147 (23.1)	
Breast	58/145 (40.0)	50/145 (34.5)	37/145 (25.5)	
GI tract	44/96 (45.8)	31/96 (32.3)	21/96 (21.9)	
Genitourinary tract	51/74 (68.9)	11/74 (14.9)	12/74 (16.2)	
Lung	28/62 (45.2)	17/62 (27.4)	17/62 (27.4)	
Brain or CNS	14/41 (34.2)	11/41 (26.8)	16/41 (39.0)	
Soft tissue or bone	11/37 (29.7)	15/37 (40.5)	11/37 (29.7)	
Gynecologic site	12/35 (34.3)	15/35 (42.9)	8/35 (22.9)	
Skin	19/26 (73.1)	5/26 (19.2)	2/26 (7.7)	
Lymph node	5/15 (33.3)	7/15 (46.7)	3/15 (20)	
Stage				.19
0 or 1	56/215 (26.0)	55/173 (31.8)	41/123 (33.3)	
2	69/215 (32.1)	39/173 (22.5)	27/123 (22.0)	
3	48/215 (22.3)	47/173 (27.2)	26/123 (21.1)	
4	42/215 (19.5)	32/173 (18.5)	29/123 (23.6)	
Dose, cGy	5040 (1000-7920)	5,82 (540-7920)	5040 (1400-7000)	.86
Metastatic at start of RT[d]	25 (8.5)	28 (12.6)	11 (6.8)	.14
Chemotherapy at or before start of RT	156 (52.9)	126 (56.8)	90 (55.9)	.65
Surgery at or before start of RT	200 (67.8)	160 (72.1)	110 (68.3)	.56

CNS, central nervous system; GI, gastrointestinal; RT, radiation therapy.

  [a] Patients rated their distress level from 0 (no distress) to 10 (extreme distress).

  [b] Continuous data are presented as median (range). Categorical data are presented as number of patients (percentage of sample).

  [c] P values are from a Kruskal-Wallis rank sum test or the Fisher exact test.

  [d] Metastatic disease information was unavailable for 1 patient.

patients was relatively similar between the moderate- and high-distress groups, as evidenced by the relatively similar HRs (1.58 and 1.42, respectively), we combined the moderate- and high-distress groups and examined the association with survival after RT. As shown in Table 3, patients with either a moderate or high distress level had significantly poorer survival than patients with low distress in both univariable analysis (HR, 1.51; P = .042) and multivariable analysis (HR, 1.57; P = .034). Survival after the start of RT is shown for the 3 distress level groups in Figure 2.

Figure 3 shows mean values for the 29 individual distress items from the PRD questionnaire (Fig 1; eTable 1, available as supplementary material online only at www.practicalradonc.org). The top 5 causes of distress were "How I feel during treatment" (mean, 2.49); "Fatigue" (mean, 2.39); "Out-of-pocket medical costs" (mean, 2.25); "Pain that affects my daily functioning" (mean, 2.24); and "Sleep difficulties" (mean, 2.23). The least worrisome concerns were "Spirituality" (mean, 1.34); "Controlling my anger" (mean, 1.40); "Transportation to treatment" (mean, 1.40); "Housing during treatment" (mean, 1.41); and "A loved one relying on me for their physical care" (mean, 1.42).

Discussion

The results of this study provide the first evidence that a higher level of patient distress before and during RT is associated with a poorer outcome after RT. Specifically, patients who had a score of 4 or more on the overall PRD level questionnaire had a 1.5-fold increased risk of death after RT compared with patients with lower scores. This translated into a 2-year survival rate of 74%, which is about 10% less than that for patients with lower scores (83%). Importantly, this finding was independent of key characteristics, including age, sex, primary cancer site, RT dose, metastatic disease, chemotherapy, and surgery; however, the possibility that other unmeasured variables influenced these results must certainly be acknowledged.

Distress screening and interventions should be implemented in all oncology centers to assess, anticipate, and alleviate suffering of patients and to improve QOL and survival. At our institution, a distress screening consultation with a certified social worker is warranted if patients rate any of the 30 items as 4 or more or if they rate their overall distress as 8 or more. A lower distress screening threshold protocol should be implemented.

Psychosocial distress related to RT has been a well-established association since the early 1980s, when studies

Table 2 Associations between baseline patient characteristics and survival after definitive RT[a]

Variable	HR[b] (95% CI)	P value
Age at start of RT (10-y increase)	1.26 (1.08-1.47)	.003
Male	1.63 (1.11-2.40)	.012
Primary cancer site		<.001
Head and neck	1.00 (reference)	NA
Breast	0.06 (0.01-0.24)	<.001
GI tract	0.94 (0.56-1.59)	.83
Genitourinary tract	0.04 (0.01-0.32)	.002
Lung	1.47 (0.85-2.56)	.17
Brain or CNS	1.23 (0.63-2.43)	.55
Soft tissue or bone	0.44 (0.15-1.23)	.12
Gynecologic site	0.71 (0.30-1.69)	.44
Skin	1.51 (0.67-3.41)	.32
Lymph node	0.47 (0.11-1.98)	.31
Stage		<.001
0 or 1	1.00 (reference)	NA
2	3.92 (1.69-9.06)	.001
3	5.73 (2.53-12.98)	<.001
4	4.37 (1.86-10.29)	<.001
Dose (1000-cGy increase)	1.01 (0.86-1.18)	.91
Metastatic at start of RT	1.19 (0.64-2.22)	.58
Chemotherapy at or before start of RT	2.38 (1.56-3.62)	<.001
Surgery at or before start of RT	0.57 (0.39-0.84)	.004

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; HR, hazard ratio; NA, not applicable; RT, radiation therapy.

[a] HRs, 95% CIs, and P values were determined from unadjusted Cox proportional hazards regression models.

[b] HRs correspond to the increase in parentheses for continuous variables and to the presence of the given characteristic for categorical variables.
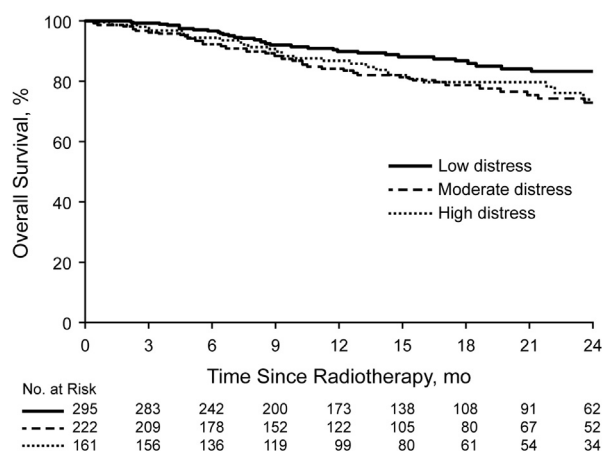

Figure 2 Survival after definitive radiation therapy according to patient-reported distress. Patients rated their distress level from 0 (no distress) to 10 (extreme distress). Low distress indicates ratings from 0 through 3; moderate distress, from 4 through 6; and high distress, from 7 through 10.

screening for patients undergoing RT is vital.[10,11] The regular use of screening leads to improved communication between patients and their health care providers.[12] However, PRD is not well appreciated by all medical providers: some consider it an inadequate and unfeasible screening tool, contrary to the patients' perspectives, which have shown moderate satisfaction with the screening process.[13-16] When cancer is diagnosed, psychosocial support should be initiated through an integrated medical collaboration.[17,18] Distress might increase during multiple cancer treatments and might peak approximately 2 weeks after the start of RT.[19] Another study suggested that other complications related to treatment, such as anxiety and depression, are highest before treatment and diminish with treatment, followed by an increase in distress symptoms up to 1 year after completion of RT.[20] This suggests that longer follow-up is needed to monitor the psychosocial status of those patients.

showed that cancer patients receiving RT are at more risk for distress and the complications that might arise from RT.[8,9] Multiple studies have suggested that routine distress

Table 3 Associations between PRD and survival after definitive RT[a]

PRD level	Survival after RT (95% CI)		Univariable analysis		Multivariable analysis[b]	
	1 y after RT	2 y after RT	HR (95% CI)	P value	HR (95% CI)	P value
As a continuous variable						
3-unit increase	NA	NA	1.34 (1.08-1.65)	.007	1.39 (1.11-1.74)	.004
As a categorical variable				.11[c]		.10[c]
Low distress, 0-3 (n = 295)	90% (86%-94%)	83% (77%-89%)	1.00 (reference)	NA	1.00 (reference)	NA
Moderate distress, 4-6 (n = 222)	84% (79%-90%)	73% (66%-81%)	1.58 (1.02-2.44)	.042	1.62 (1.03-2.56)	.038
High distress, 7-10 (n = 161)	87% (81%-93%)	74% (65%-84%)	1.42 (0.88-2.30)	.15	1.49 (0.90-2.48)	.12
Moderate or high distress, 4-10 (n = 383)	85% (81%-89%)	74% (68%-80%)	1.51 (1.02-2.24)	.042	1.57 (1.03-2.38)	.034

CI, confidence interval; HR, hazard ratio; NA, not applicable; PRD, patient-reported distress; RT, radiation therapy.

[a] HRs, 95% CIs, and P values were determined from Cox proportional hazards regression models.

[b] Multivariable models were adjusted for age, sex, primary cancer site, RT dose, metastatic disease at the start of RT, chemotherapy at or before the start of RT, and surgery at or before the start of RT.
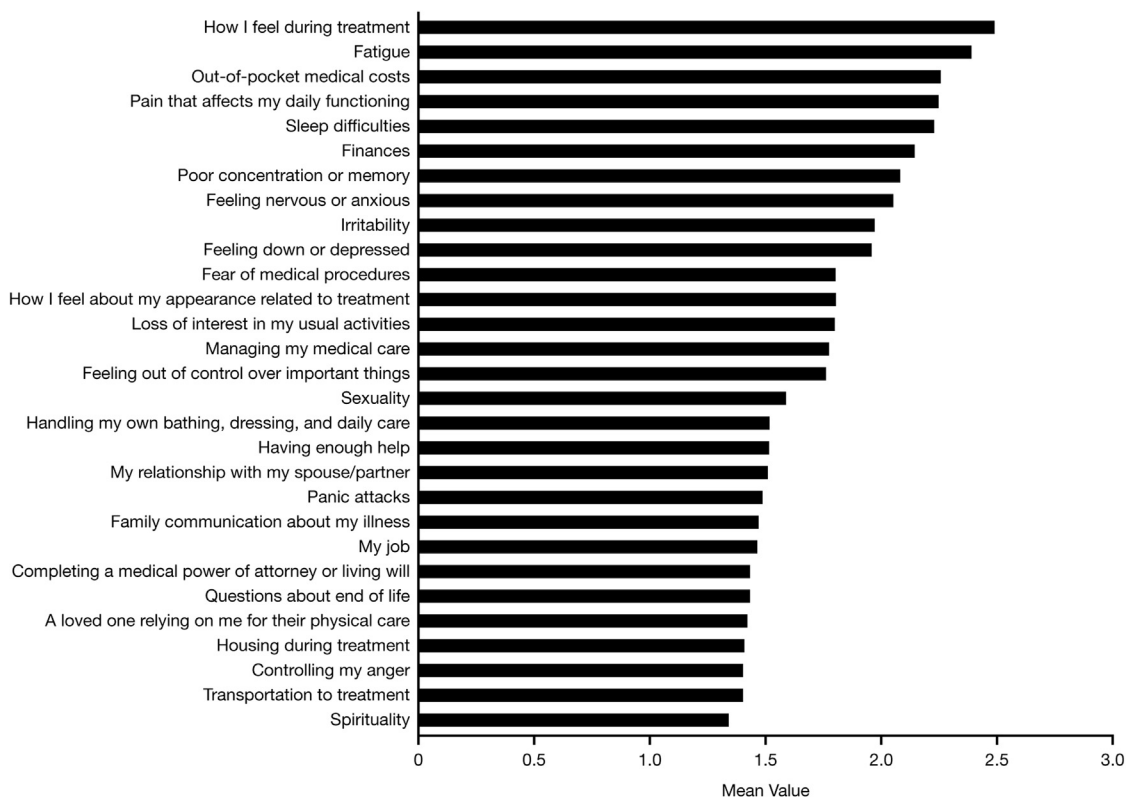
[c] Test of overall difference.

Figure 3 Mean values of responses to patient-reported distress items. Patients used each item to complete the statement "I am concerned about…" on a 5-point scale from 1 ("Not at all") to 5 ("Very much").

Psychosocial function usually decreases in about one-third of patients receiving RT who experience distress.[21] Consequently, multiple studies have suggested that short-term RT complications such as fatigue subside to baseline by week 27 after RT, and management of the patients is indicated for boosting patient self-esteem and therefore QOL.[22,23] The combination of distress screening and distress management resources availability are essential for mounting a good response to the psychosocial complications of cancer treatment.[24]

Several studies recommended different approaches for managing distress while receiving RT. Methods such as mindfulness-based intervention, yoga, and listening to music have been shown to improve overall QOL by reducing stress level and hence cortisol level.[25-27] Other techniques, such as Web-based cognitive behavioral therapy, may be more convenient for patients than traditional cognitive behavioral therapy.[28]

The top 5 causes of distress in our sample were mostly related to RT short-term side effects that would subside with time (eg, fatigue, pain, sleeping difficulties) rather than long-term complications that would have a greater effect on QOL.[29,30] Other studies have suggested that fatigue might persist and cause a chronic complication.[31] Medical cost was 1 of the top 3 concerns of patients, indicating the need to evaluate this area proactively and, when possible, to inform patients of available additional resources (eg, identifying a more affordable pharmacy through an Internet site).[32]

The 5 least distressing components in our sample were related to how patients dealt with the logistics of receiving RT, which included transportation and housing. Spirituality was identified as the least likely area to be affected by RT. Cancer patients use spirituality and faith to deal with the stress of coping with cancer.[33] Sources of PRD likely vary in different patient populations.

The main limitation of the study is the retrospective design. Another noteworthy limitation is the lack of staging information for approximately 25% of the patients in our database. As a result, we could not adjust for stage in our multivariable analysis to directly address any confounding potential that it might have. As expected, survival was markedly worse for patients with higher stage cancer; however, stage did not differ significantly among the 3 distress level groups ($P = .19$), and therefore it has limited confounding potential and would likely not alter the results of the association analysis involving PRD level and survival after RT.

Conclusion

To the best of our knowledge, this is the first study to show that an elevated level of PRD in patients receiving

definitive RT is associated with poorer outcome in the form of lower survival after treatment. PRD and survival for patients who rated their overall distress level lower than 4 had better survival than patients with higher distress levels. Timely identification and early intervention may mitigate the consequences of distress. Distress screening guidelines should be implemented for patients receiving definitive RT. Interventions for those at higher levels of distress should be further evaluated and assessed for effectiveness in reducing PRD. Radiation oncologists and all cancer specialists need to develop targeted interventions to better meet the unique needs of each patient. Further studies are needed to assess whether targeted distress intervention would help to decrease the degree of PRD and improve survival.

Supplementary data

Supplementary material for this article (http://dx.doi.org/10.1016/j.prro.2017.03.004) can be found at www.practicalradonc.org.

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