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## What Proportion of Patients With Musculoskeletal Sarcomas Demonstrate Symptoms of Depression or Anxiety?

Elizabeth M. Polfer MD<sup>1</sup>, Yesne Alici MD<sup>2</sup>, Raymond E. Baser MS<sup>3</sup> , John H. Healey MD<sup>4</sup>,  
Meredith K. Bartelstein MD<sup>4</sup>

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### Abstract

**Background** It is estimated that the 12-month prevalence of depression in the United States is 8.6%, and for anxiety it is 2.9%. Although prior studies have evaluated depression and anxiety in patients with carcinoma, few have specifically evaluated patients with sarcoma, who often have unique treatment considerations such as mobility changes after surgery.

**Questions/purposes** We evaluated patients with sarcoma seen in our orthopaedic oncology clinic to determine (1) the proportion of patients with depression symptoms, symptom severity, how many patients triggered a referral to mental health professionals based upon our prespecified cutoff scores on the nine-item Patient Health Questionnaire (PHQ-9), and if their symptoms varied by disease state; (2) the proportion of patients with anxiety symptoms, symptom severity, how many patients triggered a referral to mental health professionals based upon our prespecified cutoff scores on the seven-item Generalized Anxiety Disorder Scale (GAD-7), and if they symptoms varied by disease state; (3) whether other factors were associated with the proportion and severity of symptoms of anxiety or depression, such as tumor location in the body (axial skeleton, upper extremity, or lower extremity), general type of tumor (bone or soft tissue), specific diagnosis, use of chemotherapy, length of follow-up (less than 1 year or greater than 1 year), and gender; and (4) what proportion of patients accepted referrals to mental health professionals, when offered.

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**Methods** This study was a cross-sectional survey study performed at a single urban National Cancer Institute–designated Comprehensive Cancer Center from April 2021 until July 2021. All patients seen in the orthopaedic clinic 18 years of age and older with a diagnosis/presumed diagnosis of sarcoma were provided the PHQ-9 as well as the GAD-7 in our clinic. We did not track those who elected not to complete the surveys. Surveys were scored per survey protocol (each question was scored from 0 to 3 and summed). Specifically, PHQ-9 scores the symptoms of depression as 5 to 9 (mild), 10 to 14 (moderate), 15 to 19 (moderately severe), and 20 to 27 (severe). The GAD-7 scores symptoms of anxiety as 5

<sup>1</sup>Department of Orthopaedics, William Beaumont Army Medical Center, Fort Bliss, TX, USA

<sup>2</sup>Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA

<sup>3</sup>Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

<sup>4</sup>Orthopaedic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

E. M. Polfer , Department of Orthopaedics, William Beaumont Army Medical Center, 18511 Highlander Medics Street, Fort Bliss, TX 79918, USA, Email: Elizabeth.Polfer@gmail.com

to 9 (mild), 10 to 14 (moderate), and 15 to 21 (severe). Patients with PHQ-9 or GAD-7 scores of 10 to 14 were referred to social work and those with scores 15 or higher were referred to psychiatry. Patients with thoughts of self-harm were referred regardless of score. Patients were divided based on disease state: patients during their initial management; patients with active, locally recurrent disease; patients with active metastatic disease; patients with prior recurrence or metastatic lesions who were subsequently treated and now have no evidence of disease (considered to be patients with discontinuous no evidence of disease); patients with no evidence of disease; and patients with an active, noncancerous complication but otherwise no evidence of disease. We additionally looked at the association of gender, chemotherapy administration, and tumor location on survey responses. Data are summarized using descriptive statistics. Differences across categories of disease state were tested for statistical significance using Kruskal-Wallis tests for continuous variables and Fisher exact tests for categorical variables as well as pairwise Wilcoxon rank sum tests.

**Results** Overall, symptoms of depression were seen in 35% (67 of 190) of patients, at varying levels of severity: 19% (37 of 190) had mild symptoms, 9% (17 of 190) had moderate symptoms, 6% (12 of 190) had moderately severe symptoms, and 1% (1 of 190) had severe symptoms. Depression symptoms severe enough to trigger a referral were seen in 17% (32 of 190) of patients overall. Patients scored higher on the PHQ-9 during their initial treatment or when they had recurrent or metastatic disease, and they were more likely to trigger a referral during those timepoints as well. The mean PHQ-9 was  $5.7 \pm 5.8$  during initial treatment,  $6.1 \pm 4.9$  with metastatic disease, and  $7.4 \pm 5.2$  with recurrent disease as compared with  $3.2 \pm 4.2$  if there was no evidence of disease ( $p = 0.001$ ). Anxiety symptoms were seen in 33% (61 of 185) of patients: 17% (32 of 185) had mild symptoms, 8% (14 of 185) had moderate symptoms, and 8% (15 of 185) had severe symptoms. Anxiety symptoms severe enough to trigger a referral were seen in 16% (29 of 185) of patients overall. Patients scored higher on the GAD-7 during initial treatment and when they had recurrent disease or an active noncancerous complication. The mean GAD-7 was  $6.3 \pm 3.2$  in patients with active noncancerous complications,  $6.8 \pm 5.8$  in patients during initial treatment, and  $8.4 \pm 8.3$  in patients with recurrent disease as compared with  $3.1 \pm 4.2$  in patients with no evidence of disease ( $p = 0.002$ ). Patients were more likely to trigger a referral during initial treatment (32% [9 of 28]) and with recurrent disease (43% [6 of 14]) compared with those with no evidence of disease (9% [9 of 97]) and those with discontinuous no evidence of disease (6% [1 of 16];  $p = 0.004$ ). There was an increase in both PHQ-9 and GAD-7 scores among patients who had

chemotherapy. Other factors that were associated with higher PHQ-9 scores were location of tumor (upper extremity versus lower extremity or axial skeleton) and gender. Another factor that was associated with higher GAD-7 scores included general category of diagnosis (bone versus soft tissue sarcoma). Specific diagnosis and length of follow-up had no association with symptoms of depression or anxiety. Overall, 22% (41 of 190) of patients were offered referrals to mental health professionals; 73% (30 of 41) accepted the referral.

**Conclusion** When treating patients with sarcoma, consideration should be given to potential concomitant psychiatric symptoms. Screening, especially at the highest-risk timepoints such as at the initial diagnosis and the time of recurrence, should be considered. Further work should be done to determine the effect of early psychiatric referral on patient-related outcomes and healthcare costs.

**Level of Evidence** Level III, therapeutic study.

## Introduction

Depression is common, and it leads to disability, morbidity, and mortality. The estimated 12-month prevalence of depression in the United States is approximately 8.6% with a lifetime morbidity risk of 29.9% [12], and in patients with chronic diseases, the prevalence is increased [24]. In addition, more than half of patients with major depressive disorder have concomitant anxiety disorder, leading to more severe symptoms and increased use of healthcare resources [20]. Perhaps not surprisingly, psychiatric disorders are common among cancer patients [7] with the reported prevalence of major depression in patients with cancer ranging from 9% to 58% [5, 20, 41, 43]. Patients with cancer who have a diagnosis of depression and/or anxiety have been shown to have increased healthcare use costs [21, 22]. The increased costs are due to more non-psychiatric annual healthcare visits (average of 12 additional visits) and an increased likelihood of emergency room visits, additional hospitalizations, and 30-day readmissions [21, 22]. Anxiety and depression not only result in increased healthcare use among patients with cancer, but also they have also been associated with morbidity and mortality in this population [5, 13, 16, 29, 31, 32, 40]. There is an increase in all-cause mortality in patients with depression and breast, prostate, and head and neck cancer [5, 16, 31, 32]. In addition, preoperative anxiety has been linked to postoperative complications in patients with prostate cancer [30] and increased mortality in those with lung cancer [40].

Unfortunately, depression and anxiety are not always recognized or easily diagnosed. The depression symptoms vary in type and severity and can be confused with the symptoms of the disease itself or the treatments [44]. As a

result, not all depression is diagnosed, and therefore, many patients go untreated. For this reason, dedicated screening for depression and anxiety is useful [6]. There are many depression screening tools in the outpatient setting, some being more cumbersome than others. The Patient Health Questionnaire-9 (PHQ-9) is the depression module of the full PHQ based on the nine criteria used in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) to diagnose depression. It is an easy-to-administer questionnaire that has been validated in several settings [9, 14, 26]. It can be used to both provide a preliminary diagnosis of depression as well as grade the severity of depression symptoms. The original cutoff value of 10 was suggested for the PHQ-9 because of the balance of sensitivity and specificity, with both being 88% for diagnosing major depressive disorder [14]. A 2021 review again recommended a cutoff value of 10 to maximize combined sensitivity and specificity of 85% for both [26]. Similarly, the Generalized Anxiety Disorder Screener (GAD-7) is used to screen for symptoms of anxiety based off of DSM-IV criteria. A cutoff value of 10 has been suggested because it maximizes sensitivity (89%) and specificity (82%) [2, 34], although other studies have suggested a lower cutoff value in patients with cancer [8].

Even though prior studies have evaluated depression and anxiety in patients with carcinoma [5, 13, 16, 29, 31, 32, 40], there is a paucity of work evaluating symptoms of anxiety and depression in patients with sarcoma; studying this group separately from other patients with cancers (such as patients with carcinomas) seems important because patients with sarcoma are more likely to have musculoskeletal pain and loss of mobility, both of which may affect mental health in different ways than might carcinoma symptoms. In the work that has been done, studies focus on screening only during the initial treatment phase [28, 35]. The American Society of Clinical Oncology recommends screening for anxiety and depression at periodic times during a patient's care but only provides general recommendations. Even though the PHQ-9 and GAD-7 are validated, simple, and easy to use, patients may get burnt out completing surveys at every office visit. Therefore, more defined guidelines on who and when to screen are needed so we can selectively screen at the highest risk time point and the higher risk populations.

We evaluated patients with sarcoma seen in our orthopaedic oncology clinic to determine (1) the proportion of patients with depression symptoms, symptom severity, how many patients triggered a referral to mental health professionals based upon our prespecified cutoff scores on the nine-item PHQ-9, and if their symptoms varied by disease state; (2) the proportion of patients with anxiety symptoms, symptom severity, how many patients triggered a referral to mental health professionals based upon our prespecified cutoff scores on the seven-item GAD-7, and if their symptoms varied by disease state; (3) whether other factors were associated with the proportion and severity of symptoms of anxiety or depression,

such as tumor location in the body (axial skeleton, upper extremity, or lower extremity), general type of tumor (bone or soft tissue), specific diagnosis, use of chemotherapy, length of follow-up (less than 1 year or greater than 1 year), and gender; and (4) what proportion of patients accepted referrals to mental health professionals, when offered.

## Patients and Methods

### *Study Design and Setting*

This study was a cross-sectional survey study from April 2021 to July 2021 at a single urban National Cancer Institute–designated Comprehensive Cancer Center with six operative orthopaedic oncologists. All patients seen in the clinic during the study period had their records reviewed before their arrival to clinic. All patients meeting the inclusion criteria (see *Participants*) were invited to fill out the surveys upon check-in to the clinic. We sought to enroll at least 150 patients during our 4-month enrollment period.

### *Participants*

We screened all patients seen in the orthopaedic clinic during the study period (April 2021 to July 2021) for inclusion. Inclusion criteria were diagnosis (tissue diagnosis) or presumed diagnosis of sarcoma (that is, patients at their initial visit for presumed sarcoma but still pending biopsy), age 18 years and older, and proficiency in the English language. Patients were excluded if they had already completed the surveys earlier in the study time frame. All patients who met inclusion criteria were provided the surveys, regardless of gender. We did not follow those who did not return the surveys.

### *Patients' Descriptive Data*

In all, 190 patients completed the PHQ-9 screen and 185 patients completed the GAD-7 screen. A total of 51% (97 of 190) were men, and the median (IQR) ages at the time of biopsy and follow-up were 51 years (28 to 64) and 56 years (36 to 68), respectively. Most (53% [100 of 190]) patients presented with no evidence of disease, followed by metastatic disease (13% [25 of 190]) (Table 1).

### *Description of Experiment, Treatment, or Surgery*

After agreeing to participate, patients completed two surveys: the PHQ-9 and the GAD-7. The survey responses were reviewed within 72 hours. Surveys were scored per survey protocol; each question was scored from 0 (meaning no

**Table 1.** Patient characteristics (n =190 patients)

Characteristic	Overall (n = 190)	Initial (n = 29)	Recurrent (n = 14)	Metastatic (n = 25)	dNED (n = 16)	NED (n = 100)	acNED (n = 6)	p value
Gender								0.93
Women	49% (93)	48% (14)	57% (8)	44% (11)	50% (8)	48% (48)	67% (4)	
Men	51% (97)	52% (15)	43% (6)	56% (14)	50% (8)	52% (52)	33% (2)	
Length of follow-up								
> 1 year	68% (130)	3.4% (1)	86% (12)	80% (20)	88% (14)	77% (77)	100% (6)	
≤ 1 year	32% (60)	97% (28)	14% (2)	20% (5)	13% (2)	23% (23)	0% (0)	
Location								0.89
Bone	46% (87)	45% (13)	36% (5)	44% (11)	44% (7)	47% (47)	67% (4)	
Soft tissue	54% (103)	55% (16)	64% (9)	56% (14)	56% (9)	53% (53)	33% (2)	
Skeletal location								< 0.001
Axial	18% (35)	28% (8)	29% (4)	28% (7)	13% (2)	13% (13)	17% (1)	
Lower	44% (84)	59% (17)	57% (8)	56% (14)	38% (6)	34% (34)	83% (5)	
Upper	37% (71)	14% (4)	14% (2)	16% (4)	50% (8)	53% (53)	0% (0)	
Diagnosis								
Chondrosarcoma	17% (32)	7% (2)	14% (2)	16% (4)	19% (3)	21% (21)	0% (0)	
Ewing sarcoma	6% (11)	10% (3)	0% (0)	4% (1)	6% (1)	4% (4)	33% (2)	
Liposarcoma	6% (11)	14% (4)	14% (2)	0% (0)	0% (0)	3% (3)	33% (2)	
Myxofibrosarcoma	7% (13)	0% (0)	7% (1)	4% (1)	19% (3)	8% (8)	0% (0)	
Osteosarcoma	13% (25)	0% (0)	7% (1)	12% (3)	25% (4)	16% (16)	17% (1)	
Synovial sarcoma	5% (10)	7% (2)	7% (1)	8% (2)	6% (1)	4% (4)	0% (0)	
UPS	12% (23)	10% (3)	7% (1)	36% (9)	6% (1)	9% (9)	0% (0)	
Other	32% (65)	52% (15)	43% (6)	20% (5)	19% (3)	35% (35)	17% (1)	
Chemotherapy								< 0.001
No	54% (93 of 171)	10% (1 of 10)	50% (7)	12% (3)	56% (9)	72% (72)	17% (1)	
Yes	46% (78 of 171)	90% (9 of 10)	50% (7)	88% (22)	44% (7)	28% (28)	83% (5)	
Unknown	19	19	0	0	0	0	0	

Data presented as % (n). Some categories may not sum to 100% due to rounding; dNED = discontinuous no evidence of disease; acNED = active complication but no evidence of disease; NED = no evidence of disease; UPS = undifferentiated pleomorphic sarcoma.

symptoms in the past 2 weeks) to 3 (meaning symptoms nearly every day) and then summed. The range of potential scores for the PHQ-9 is 0 to 27, and the range of potential scores for the GAD-7 is 0 to 21. Specifically, the PHQ-9 defines depression symptoms based on score: 5 to 9 (mild), 10 to 14 (moderate), 15 to 19 (moderately severe), and 20 to 27 (severe). The GAD-7 defines symptoms of anxiety based on score: 5 to 9 (mild), 10 to 14 (moderate), and 15 to 21 (severe) [14, 34, 36]. The minimum clinically important difference for the PHQ-9 has been reported from 3.0 to 3.7, and for the GAD-7 from 3.3 to 4 [3, 19, 38].

#### *Variables, Outcome Measures, Data Sources, and Bias*

There is debate on the recommended diagnostic cutoff values for the PHQ-9 and GAD-7. Published cutoff values

have ranged from 7 to 15 for the GAD-7 and 8 to 15 for the PHQ-9 [8, 14, 25, 26, 34, 36]. We elected for a cutoff value of 10 based on sensitivity and specificity for the diagnosis of major depressive disorder and generalized anxiety disorder [8, 14, 15, 26] when creating for the criteria referral to a mental health provider. As a result, for both the PHQ-9 and GAD-7, patients with scores of 10 to 14 were referred to social work and those with scores of 15 or higher were referred to psychiatry. Referral acceptance was determined by contact between social work or psychiatry and the patient as documented in the medical record. If there was concern about self-harm (a patient answering affirmative to question 9 on the PHQ-9, which inquires about thoughts of self-harm), as a safety measure, the clinic nurse would promptly follow up with the patient to administer the Columbia Suicide Severity Rating Scale, the results of which determined whether the patient should be referred to

**Table 2.** PHQ-9 scores by disease state at the time of survey

Scores	Overall (n = 190)	Initial (n = 29)	Recurrent (n = 14)	Metastatic (n = 25)	dNED (n = 16)	NED (n = 100)	acNED (n = 6)	p value
PHQ-9 total score	4.4 ± 4.8	5.7 ± 5.8	7.4 ± 5.2	6.1 ± 4.9	3.9 ± 4.7	3.2 ± 4.2	5.0 ± 4.3	0.001
PHQ-9 depression severity								
Minimal	65% (123)	52% (15)	36% (5)	48% (12)	69% (11)	76% (76)	67% (4)	
Mild	20% (37)	24% (7)	29% (4)	24% (6)	19% (3)	16% (16)	17% (1)	
Moderate	9% (17)	14% (4)	21% (3)	16% (4)	6% (1)	4% (4)	17% (1)	
Moderately severe	6% (12)	10% (3)	14% (2)	12% (3)	6% (1)	3% (3)	0% (0)	
Severe	1% (1)	0% (0)	0% (0)	0% (0)	0% (0)	1% (1)	0% (0)	
PHQ-9 cutoff								0.01
< 10	84% (160)	76% (22)	64% (9)	72% (18)	87% (14)	92% (92)	83% (5)	
≥ 10	16% (30)	24% (7)	36% (5)	28% (7)	13% (2)	8% (8)	17% (1)	
PHQ-9								0.005
No symptoms (score 0)	26% (49)	24% (7)	7% (1)	4% (1)	31% (5)	35% (35)	0% (0)	
Symptoms	74% (141)	76% (22)	93% (13)	96% (24)	69% (11)	65% (65)	100% (6)	

Data presented as mean ± SD or % (n). Some categories may not sum to 100% due to rounding; dNED = discontinuous no evidence of disease; NED = no evidence of disease; acNED = active complication but no evidence of disease.

social work, psychiatry, or the nearest emergency department, per hospital policy.

Patients were categorized based on their disease state at the time of their survey response: initial management, locally recurrent disease, metastatic disease, discontinuous no evidence of disease, active noncancerous complication, or no evidence of disease. The initial treatment group consisted of patients during their initial treatment course (initial work up, neoadjuvant/adjuvant chemotherapy and/or radiation, surgery). All but one patient in the initial treatment group was less than 1 year since diagnosis; the one patient outlier was at 14 months because of treatment delay due to the COVID-19 pandemic. Patients with locally recurrent disease were defined as patients who were initially treated, were considered to have no evidence of disease, and now have actively recurrent local disease. Patients with metastatic disease were defined as patients with active metastatic disease from the initial sarcoma. Patients with discontinuous no evidence of disease were defined as patients who underwent initial treatment, had a period of no disease after initial treatment, then subsequently had either locally recurrent disease or metastatic lesions that was then subsequently treated, and once again have no evidence of disease. Patients with active complications were defined as patients who had no evidence of disease but who had an active complication resulting in surgery such as fracture, implant failure, or infection.

Additional information gathered included the tumor location on the skeleton (upper extremity, lower extremity, or axial skeleton), general sarcoma diagnosis (bone

sarcoma versus soft tissue sarcoma), specific diagnosis (sarcoma subtype), gender, and follow-up length (less than 1 year versus greater than or equal to 1 years).

#### *Ethical Approval*

This study's protocol was reviewed by the human research protection program of our institution and was determined to meet the criteria for an exempt study based on institutional criteria for work with interactions only involving the use of survey procedures.

#### *Statistical Analysis and Study Size*

We estimated enrolling a minimum of 150 patients during our 4-month enrollment period. Given our minimum expected sample size of 150 and our descriptive primary aim, we a priori calculated the precision with which we could estimate our primary endpoint, which was the proportion of sarcoma patients seen in our orthopaedic oncology clinic with moderate or worse depression symptoms. Specifically, assuming the proportion of patients with moderate or worse depression on the PHQ-9 would be between 10% and 15%, a sample size of 150 patients would allow us to estimate this proportion with a 95% confidence interval (CI) half-width between 4.8% and 5.7%, respectively. Patient characteristics, as well as the PHQ-9 and GAD-7 scores and clinical categories, have

been summarized using descriptive statistics. PHQ-9 and GAD-7 descriptive statistics have been presented for the overall sample as well as by disease state. We tested for differences in continuous PHQ-9 and GAD-7 scores across categories of disease state using Kruskal-Wallis tests as well as performed pairwise Wilcoxon rank sum tests. We used Fisher exact tests to assess differences across disease states in the PHQ-9 and GAD-7 clinical categories, whether a referral was offered, and whether a referral was accepted among those offered a referral. Five patients did not complete the GAD-7 and were excluded from analyses of the GAD-7 variables, but they were included in the PHQ-9 analyses.

**Results**

*Symptoms of Depression and Referral to Mental Health Professionals*

Symptoms of depression were seen in 35% (67 of 190) of patients at varying levels of severity: 19% (37 of 190) had mild symptoms, 9% (17 of 190) had moderate symptoms, 6% (12 of 190) had moderately severe symptoms, and 1% (1 of 190) had severe symptoms. Depression symptoms severe enough to trigger a referral were seen in 17% (32 of 190) of patients overall. Patients scored higher on the PHQ-9 during their initial treatment and with recurrent or metastatic disease and were more likely to trigger a referral during those timepoints as well. The mean ± SD for the

PHQ-9 was 5.7 ± 5.8 during initial treatment, 6.1 ± 4.9 with metastatic disease, and 7.4 ± 5.2 with recurrent disease compared with 3.2 ± 4.2 if there was no evidence of disease (p = 0.001). Only 26% (49 of 190) of patients had no depression symptoms. Patients were more likely to have no symptoms if they had no evidence of disease (35% [35 of 100]) or discontinuous no evidence of disease (31% [5 of 16]) compared with the other disease states (p = 0.005). All patients with an active noncancerous complication had depression symptoms. A referral to mental health was triggered in 36% (5 of 14) of patients with recurrent disease, 28% (7 of 25) of patients with metastatic disease, and 24% (7 of 29) of patients during their initial treatment compared with 8% (8 of 100) of patients with no evidence of disease (p = 0.01) (Table 2).

*Symptoms of Anxiety and Referral to Mental Health Professionals*

Anxiety symptoms were seen in 33% (61 of 185) of patients; 17% (32 of 185) had mild symptoms, 8% (14 of 185) had moderate symptoms, and 8% (15 of 185) had severe symptoms. Anxiety symptoms severe enough to trigger a referral were seen in 16% (29 of 185) of patients overall (Table 3). Patients during their initial treatment, patients with recurrent disease, and patients with active noncancerous complications had increased mean scores ± SD on the GAD-7 (6.8 ± 5.8, 8.4 ± 8.3, and 6.3 ± 3.2, respectively) compared with patients with no evidence of

**Table 3.** GAD-7 scores by disease state at the time of survey

Scores	Overall (n = 185)	Initial (n = 28)	Recurrent (n = 14)	Metastatic (n = 24)	dNED (n = 16)	NED (n = 97)	acNED (n = 6)	p value
GAD-7 total score	4.3 ± 5.2	6.8 ± 5.8	8.4 ± 8.3	4.3 ± 4.8	3.1 ± 4.2	3.1 ± 4.2	6.3 ± 3.2	0.002
GAD-7 depression severity								
Minimal	67% (124)	50% (14)	50% (7)	71% (17)	69% (11)	76% (74)	17% (1)	
Mild	17% (32)	18% (5)	7% (1)	17% (4)	25% (4)	14% (14)	67% (4)	
Moderate	8% (14)	21% (6)	7% (1)	4% (1)	0% (0)	5% (5)	17% (1)	
Severe	8% (15)	11% (3)	36% (5)	8% (2)	6% (1)	4% (4)	0% (0)	
GAD-7 cutoff								0.004
< 10	84% (156)	68% (19)	57% (8)	87% (21)	94% (15)	91% (88)	83% (5)	
≥ 10	16% (29)	32% (9)	43% (6)	13% (3)	6% (1)	9% (9)	17% (1)	
GAD-7								0.01
No symptoms (Score 0)	29% (54)	11% (3)	14% (2)	21% (5)	44% (7)	38% (37)	0% (0)	
Symptoms	71% (131)	89% (25)	86% (12)	79% (19)	56% (9)	62% (60)	100% (6)	

Data presented as mean ± SD or % (n). Some categories may not sum to 100% due to rounding; dNED = discontinuous no evidence of disease; NED = no evidence of disease; acNED = active complication but no evidence of disease.

disease ( $3.1 \pm 4.2$ ;  $p = 0.002$ ). Similar to what was seen with depression symptoms, only 29% (54 of 185) had no anxiety symptoms. Patients with no evidence of disease (38% [37 of 97]) and discontinuous no evidence of disease (44% [7 of 16]) were more likely to have no symptoms ( $p = 0.01$ ), and all patients with an active complication had symptoms. Additionally, patients were more likely to have severe enough symptoms to trigger a referral to mental health during their initial treatment (32% [9 of 28]) and with recurrent disease (43% [6 of 14]) compared with those with no evidence of disease (9% [9 of 97];  $p = 0.004$ ).

#### *Factors Associated With Depressive and Anxious Symptoms*

Overall, the mean  $\pm$  SD for the PHQ-9 score was  $4.4 \pm 4.9$  and the mean GAD-7 score was  $4.2 \pm 5.2$ . Patients who underwent chemotherapy for treatment of their disease

were more likely to have depression symptoms than those who did not have chemotherapy (86% [67 of 78] versus 65% [60 of 93];  $p = 0.001$ ) and more likely to have higher PHQ-9 and GAD-7 scores. The mean  $\pm$  SD PHQ-9 score was  $5.7 \pm 5.1$  if patients underwent chemotherapy versus  $3.4 \pm 4.5$  if they did not ( $p < 0.001$ ) (Table 4). Similarly, GAD-7 scores were higher ( $5.3 \pm 5.6$  versus  $3.2 \pm 4.4$ ) with the use of chemotherapy ( $p = 0.005$ ). PHQ-9 scores were also higher in patients with tumor location in the axial skeleton or lower extremity compared with upper extremity; they were also higher in women. The mean  $\pm$  SD PHQ-9 score was  $5.8 \pm 5.4$  in patients with tumors in the axial skeleton and  $4.9 \pm 4.8$  for tumors in the lower extremity compared with  $3.1 \pm 4.3$  for tumors in the upper extremity ( $p = 0.003$ ) (Table 5). The mean  $\pm$  SD PHQ-9 was  $5.1 \pm 5.2$  for women and  $3.6 \pm 4.3$  for men ( $p = 0.03$ ) (Table 6). Additionally, GAD-7 scores were associated with tumor type (soft tissue versus bone). Higher GAD-7 scores were seen in patients with bone sarcomas compared with soft

**Table 4.** PHQ-9 and GAD-7 scores as a function of chemotherapy

	Overall (n = 171)	No (n = 93)	Yes (n = 78)	p value
PHQ-9 total score	$4.4 \pm 4.9$	$3.4 \pm 4.5$	$5.7 \pm 5.1$	< 0.001
PHQ-9 severity				0.01
Minimal	64% (110)	71% (66)	56% (44)	
Mild	19% (33)	20% (19)	18% (14)	
Moderate	9% (16)	3% (3)	17% (13)	
Moderately severe	6% (11)	4% (4)	9% (7)	
Severe	0.6% (1)	1% (1)	0% (0)	
PHQ-9 cutoff				0.003
< 10	84% (143)	91% (85)	74% (58)	
$\geq 10$	16% (28)	9% (8)	26% (20)	
PHQ-9				0.001
No symptoms (score 0)	26% (44)	35% (33)	14% (11)	
Symptoms	74% (127)	65% (60)	86% (67)	
GAD-7 total score	$4.2 \pm 5.1$	$3.2 \pm 4.4$	$5.3 \pm 5.6$	0.005
Missing	4	1	3	
GAD-7 severity				0.12
Minimal	68% (114 of 167)	76% (70 of 92)	59% (44 of 75)	
Mild	17% (29 of 167)	13% (12 of 92)	23% (17 of 75)	
Moderate	7% (11 of 167)	5% (5 of 92)	8% (6 of 75)	
Severe	8% (13 of 167)	5% (5 of 92)	11% (8 of 75)	
GAD-7 cutoff				0.15
< 10	86% (143 of 167)	89% (82 of 92)	81% (61 of 75)	
$\geq 10$	14% (24 of 167)	11% (10 of 92)	19% (14 of 75)	
GAD-7				0.03
No symptoms (score 0)	31% (52 of 167)	38% (35 of 92)	23% (17 of 75)	
Symptoms	69% (115 of 167)	62% (57 of 92)	77% (58 of 75)	

Data presented as mean  $\pm$  SD or % (n). Some categories may not sum to 100% due to rounding.

**Table 5.** PHQ-9 and GAD-7 scores as a function of location of tumor (axial skeleton, lower extremity, or upper extremity)

	Overall (n = 190)	Axial skeleton (n = 35)	Lower extremity (n = 84)	Upper extremity (n = 71)	p value
PHQ-9 total score	4.4 ± 4.8	5.8 ± 5.4	4.9 ± 4.8	3.1 ± 4.3	0.003
PHQ-9 severity					0.16
Minimal	65% (123)	54% (19)	60% (50)	76% (54)	
Mild	19% (37)	26% (9)	20% (17)	15% (11)	
Moderate	9% (17)	11% (4)	12% (10)	4% (3)	
Moderately severe	6% (12)	9% (3)	8% (7)	3% (2)	
Severe	1% (1)	0% (0)	0% (0)	1% (1)	
PHQ-9 cutoff					0.10
< 10	84% (160)	80% (28)	80% (67)	92% (65)	
≥ 10	16% (30)	20% (7)	20% (17)	9% (6)	
PHQ-9					0.004
No symptoms (score 0)	26% (49)	20% (7)	17% (14)	39% (28)	
Symptoms	74% (141)	80% (28)	83% (70)	61% (43)	
GAD-7 total score	4.3 ± 5.2	5.4 ± 6.4	4.6 ± 4.9	3.5 ± 4.8	0.11
Missing	5	1	2	2	
GAD-7 severity					0.20
Minimal	67% (124 of 185)	62% (21 of 34)	61% (50 of 82)	77% (53 of 69)	
Mild	17% (32 of 185)	18% (6 of 34)	23% (19 of 82)	10% (7 of 69)	
Moderate	7% (14 of 185)	6% (2 of 34)	10% (8 of 82)	6% (4 of 69)	
Severe	8% (15 of 185)	15% (5 of 34)	6% (5 of 82)	7% (5 of 69)	
GAD-7 cutoff					0.61
< 10	84% (156 of 185)	79% (27 of 34)	84% (69 of 82)	87% (60 of 69)	
≥ 10	16% (29 of 185)	21% (7 of 34)	16% (13 of 82)	13% (9 of 69)	
GAD-7					0.14
No symptoms (score 0)	29% (54 of 185)	26% (9 of 34)	23% (19 of 82)	38% (26 of 69)	
Symptoms	71% (131 of 185)	74% (25 of 34)	77% (63 of 82)	62% (43 of 69)	

Data presented as mean ± SD or % (n). Some categories may not sum to 100% due to rounding.

tissue sarcomas (5.3 ± 5.5 versus 3.5 ± 4.8; p = 0.015) (Table 7). There was no difference seen in either PHQ-9 or GAD-7 scores with specific tissue diagnosis (chondrosarcoma, osteosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, or other) or length of follow-up (longer than 12 months compared with follow-up of less than 1 year).

*Do Patients Accept Referrals to Mental Health When Offered?*

Overall, 22% (41 of 190) of patients were offered referrals to mental health services (social work or psychiatry), of whom 73% (30 of 41) accepted the referrals. When evaluating self-harm, we found that 7% (13 of 190) of patients

had thoughts of hurting themselves or considered themselves as being better off dead within 2 weeks of their visit. Of the patients who reported thoughts of self-harm, 77% (10 of 13) scored above the threshold to trigger a referral on the PHQ-9, and 67% (8 of 12) of patients who completed the GAD-7 scored above the threshold to trigger a referral. Only two patients would not have otherwise triggered a referral.

**Discussion**

Depression and anxiety are not always recognized or easily diagnosed, especially in patients with cancer. Depression symptoms vary in type and severity, and they can overlap with the symptoms of cancer or its treatment. As a result, not all patients with depression and anxiety symptoms are

**Table 6.** PHQ-9 and GAD-7 scores as a function of gender

	Overall (n = 190)	Women (n = 93)	Men (n = 97)	p value
PHQ-9 total score	4.4 ± 4.8	5.1 ± 5.2	3.6 ± 4.3	0.03
PHQ-9 severity				0.22
Minimal	65% (123)	61% (57)	68% (66)	
Mild	19% (37)	17% (16)	22% (21)	
Moderate	9% (17)	13% (12)	5% (5)	
Moderately severe	6% (12)	8% (7)	5% (5)	
Severe	1% (1)	1% (1)	0% (0)	
PHQ-9 cutoff				0.03
< 10	84% (160)	78% (73)	90% (87)	
≥ 10	16% (30)	22% (20)	10% (10)	
PHQ-9				0.047
No symptoms (score 0)	26% (49)	19% (18)	32% (31)	
Symptoms	74% (141)	81% (75)	68% (66)	
GAD-7 total score	4.3 ± 5.2	4.9 ± 5.2	3.8 ± 5.2	0.08
GAD-7 severity				0.12
Minimal	67% (124 of 185)	59% (54 of 91)	74% (70 of 94)	
Mild	17% (32 of 185)	21% (19 of 91)	14% (13 of 94)	
Moderate	8% (14 of 185)	11% (10 of 91)	4% (4 of 94)	
Severe	8% (15 of 185)	9% (8 of 91)	7% (7 of 94)	
GAD-7 cutoff				0.13
< 10	84% (156 of 185)	80% (73 of 91)	88% (83 of 94)	
≥ 10	16% (29 of 185)	20% (18 of 91)	12% (11 of 94)	
GAD-7				0.25
No symptoms (score 0)	29% (54 of 185)	25% (23 of 91)	33% (31 of 94)	
Symptoms	71% (131 of 185)	75% (68 of 91)	67% (63 of 94)	

Data presented as mean ± SD or % (n). Some categories may not sum to 100% due to rounding.

diagnosed, and many patients go without treatment, which can lead to increased healthcare use and morbidity and up to a fourfold increase in mortality [5, 7, 17, 22, 24, 41]. Given the increase in morbidity and mortality associated with anxiety and depression, and because patients with sarcoma may have physical symptoms such as musculoskeletal pain and loss of mobility that are distinct from patients with other kinds of cancers, we sought to determine timepoints in care associated with increased symptoms of anxiety and depression as well as patient- and disease-specific factors associated with increased symptoms to allow for more effective screening. This study demonstrated that patients during their initial treatment and patients with recurrent or metastatic disease had increased depression symptoms as measured by the PHQ-9 and patients during their initial treatment and patients with recurrent disease had increased anxiety symptoms as measured by the GAD-7. We also demonstrated factors such as being a woman, use of chemotherapy, location of sarcoma in axial skeleton or lower extremity as opposed to upper extremity, and having a

bone sarcoma as opposed to a soft tissue sarcoma were associated with increased symptoms of anxiety and/or depression. Knowing when a patient is at risk for having increased symptoms of depression or anxiety would allow the surgeon to appropriately screen and refer the patient for additional care.

#### Limitations

The limitations of this study include the possibility of both under- and over-identifying depression or anxiety based on the self-reported survey scores and our limited sample size. We theorize that patients may underreport symptoms for fear of being identified as having a mental health problem. Additionally, there are several cutoff values for the GAD-7 and PHQ-9, with some as low as 7 for patients with cancer [8, 11, 36]; however, other studies suggest a higher cutoff value to maximize the balance between sensitivity and specificity [2, 15, 26]. We elected to use the cutoff value of 10 to decrease false positives to minimize this limitation.

**Table 7.** PHQ-9 and GAD-7 scores as a function of location of tumor (soft tissue or bone)

	Overall (n = 190)	Bone (n = 87)	Soft tissue (n = 103)	p value
PHQ-9 total score	4.4 ± 4.8	4.9 ± 5.1	3.9 ± 4.6	0.13
PHQ-9 severity				0.90
Minimal	65% (123)	62% (54)	67% (69)	
Mild	19% (37)	21% (18)	18% (19)	
Moderate	9% (17)	10% (9)	8% (8)	
Moderately severe	6% (12)	7% (6)	6% (6)	
Severe	1% (1)	0% (0)	1% (1)	
PHQ-9 cutoff				0.61
< 10	84% (160)	83% (72)	85% (88)	
≥ 10	16% (30)	17% (15)	15% (15)	
PHQ-9				0.25
No symptoms (score 0)	26% (49)	22% (19)	29% (30)	
Symptoms	74% (141)	78% (68)	71% (73)	
GAD-7 total score	4.3 ± 5.2	5.3 ± 5.5	3.5 ± 4.8	0.015
GAD-7 severity				0.06
Minimal	67% (124 of 185)	58% (49 of 85)	75% (75 of 100)	
Mild	17% (32 of 185)	21% (18 of 85)	14% (14 of 100)	
Moderate	8% (14 of 185)	12% (10 of 85)	4% (4 of 100)	
Severe	8% (15 of 185)	9% (8 of 85)	7% (7 of 100)	
GAD-7 cutoff				0.06
< 10	84% (156 of 185)	79% (67 of 85)	89% (89 of 100)	
≥ 10	16% (29 of 185)	21% (18 of 85)	11% (11 of 100)	
GAD-7				0.22
No symptoms (score 0)	29% (54 of 185)	25% (21 of 85)	33% (33 of 100)	
Symptoms	71% (131 of 185)	75% (64 of 85)	67% (67 of 100)	

Data presented as mean ± SD or % (n).

There is an overlap of symptoms among depression, cancer, and cancer treatment [10]. The questions in the PHQ-9 ask about energy, appetite, and concentration, which can be affected by the cancer and/or treatment. Further, these surveys screen for symptoms of depression and anxiety; a positive screening triggering a referral does not necessarily equate to a clinical diagnosis of depression or anxiety. There is no perfect screening survey; however, despite the debate over cutoff values and potential overlap in symptoms, the surveys have been validated in several settings, to include in patients with cancer, and are acceptable to use.

Additionally, our study surveyed all patients with sarcoma presenting to the orthopaedic clinic. We did not exclude patients with a preexisting diagnosis of depression and/or anxiety nor do we have comparisons to prediagnosis symptoms of depression and/or anxiety. Therefore, we cannot account for how a sarcoma diagnosis or disease state might have changed a patient’s baseline levels of symptoms. Still, we believe that our convenience sample still highlights that symptoms of depression and anxiety are common in our patient population.

Another limitation in this study was sample size. However, our sample was large enough to resolve between-group differences. Future, larger (and perhaps multicenter) studies should seek to validate or refute our findings.

Finally, we were unable to accurately record the number of patients who declined to participate in this study. Nonresponders may be different from responders, and therefore this is an additional limitation of our work. However, many of our patients responded so we feel these findings are valid, and overall, we feel that we surveyed enough patients to show that symptoms of anxiety and depression are frequent in our patients.

*Symptoms of Depression and Referral to Mental Health Professionals*

We found 74% (141 of 190) of patients had some level of depression symptoms (minimal to severe), with 35% (67 of 190) of our patients considered to have symptoms of mild or higher, and 17% (32 of 190) were severe enough to

trigger a referral to mental health professionals. Depression symptoms were highest in patients during their initial treatment and in patients with recurrent and metastatic disease. Additionally, patients were more likely to trigger a referral during those points. This study demonstrates that depression symptoms are common among patients treated for sarcoma in the orthopaedic clinic, and that there are times during care when the proportion of patients with depression symptoms is higher than others, such as at initial diagnosis and if there is local recurrence or metastatic disease. Knowing the key points to identify patients who are at-risk for depression and refer for treatment is beneficial to potentially provide care when patients need it most. Underrecognized depression in the orthopaedic clinic has been documented, with 1 in 8 patients presenting to a hand surgeon had untreated or undertreated symptoms of anxiety and depression [27]. Underrecognition and undertreatment are also common in the cancer setting. One study reported that 73% of patients with cancer who had major depression were not receiving any treatment, 24% were taking antidepressants, and only 5% were seeing a mental health professional [41]. This is important because depression has been shown to correlate with increased pain and disability and worse patient-reported outcomes/satisfaction after nononcologic orthopaedic surgery [4, 18, 37, 39, 46] as well lead to increases in all-cause mortality [16, 17, 31] and higher rates of suicide [23, 33, 45] in patients with cancer. One study looked at suicide rates among people with cancer and found the incidence of suicide to be 31.4 per 100,000 person-years, which is nearly twice as high as the national average of 16.7 per 100,000 person-years [23]. Another study specifically evaluated patients with bone and soft tissue cancer, and those authors found that the suicide rate in that population was twice as high as in the age-adjusted, race-adjusted, and gender-adjusted US general population [33]. In our patients with sarcoma, 7% (13 of 190) of patients responded that they had had thoughts of self-harm within the 2 weeks before their visit, which is similar to the published 5% proportion of suicidal ideation in patients with sarcoma [35]. Once patients at risk for depression are identified and screened, further work is needed to determine the most appropriate intervention and timing of the intervention.

#### *Symptoms of Anxiety and Referral to Mental Health Professionals*

This study showed that 71% (131 of 185) of patients with sarcoma seen in the orthopaedic clinic demonstrated some level of anxiety symptoms, with 33% (61 of 185) having mild or higher symptoms and 16% (29 of 185) having symptoms severe enough to trigger a referral. Anxiety symptoms were highest in patients during their initial

treatment, in those with recurrent disease, and in patients with active noncancerous complications. All patients with active complications demonstrated symptoms of both anxiety and depression. Patients were more likely to trigger a referral for their symptoms of anxiety during the initial treatment and when they had recurrent disease than at other timepoints and statuses. Anxiety symptoms are common among patients with sarcoma; consequently, patients should be appropriately screened and treated. Prior research has demonstrated that anxiety has been linked to higher complications in patients with prostate cancer [30] and to an increase in all-cause mortality in non-small cell lung cancer [40] and breast cancer [42]. Although the above studies have focused on patients during their initial treatment, we found that patients with recurrent disease had the highest GAD-7 scores of all our groups and resulted in more referrals. This highlights the need for ongoing patient screening, not only at the initial presentation, but also at the time of recurrence. Although evidence suggests there is a decrease in anxiety and depression 1 year after diagnosis [5], there is additional evidence to suggest that the symptoms of anxiety and depression in a cancer population do not increase or decrease at a constant rate over time, they can be unpredictable or irregular [1]. Our study suggests that an ongoing mental health evaluation is important because multiple high-risk points exist.

Although our study identified that only 16% (29 of 185) of patients had anxiety scores high enough to trigger a referral by our guidelines, another study has stated there was probable anxiety and depression in 34% of their cohort [5]. The difference could have been a function of the different screening methods as well as our elevated cutoff value. We recommend, at minimum, screening patients for anxiety symptoms during their initial treatment, and if they have recurrent disease. Further work should be done on investigating interventions, timing of interventions, and if decreasing symptoms of anxiety leads to better patient-reported outcomes.

#### *Factors Associated With Depressive and Anxious Symptoms*

Overall, we found elevated PHQ-9 scores in patients who were women, patients who underwent chemotherapy, and patients who had a tumor located in the axial skeleton or lower extremity. In addition, GAD-7 scores were elevated in patients who underwent chemotherapy and had a bone sarcoma. There was no difference noted based on specific tissue diagnosis, nor on follow-up greater than 1 year. With the identification of additional risk factors, screening can be better tailored to each individual patient. As noted above, the incidence of suicide is higher among patients with bone and soft tissue sarcomas compared with the

general US population [23, 33, 45]. One study went on to describe risk factors for suicide, which included being a man, tumors in the vertebral column, tumors in the pelvic bones, and in patients within the first 5 years of diagnosis [33]. We similarly found higher PHQ-9 scores in patients with tumors in the axial skeleton and during initial treatment, but we found higher PHQ-9 scores in women compared with men. Additionally, of our 13 patients who had thoughts of self harm, nine were women. We recommend consideration of more frequent screening of patients who are treated with chemotherapy, have tumors of the axial skeleton or lower extremity, and have bone sarcomas.

### *Do Patients Accept Referrals to Mental Health When Offered?*

There are many tools for screening for depression and anxiety in the outpatient setting, with some being more cumbersome than others. We elected to use the PHQ-9 and the GAD-7 because they are easy to administer and have been validated in several settings to include the cancer population [8, 9, 15]. With a cutoff value of 10, we referred 22% (41 of 190) of patients to either social work or psychiatry, and nearly three-fourths of these patients (73% [30 of 41]) accepted the referrals. Referral acceptance was determined by contact between social work or psychiatry and the patient, as documented in the medical record. Future work will involve greater follow-up on those patients who accepted referrals and participated in mental health follow-up. Although not fully evaluable with the survey scores, we noticed these surveys were met with a generally positive response. Some patients even expressed gratitude for asking these questions, either in person during the visit or by writing in the survey margins.

### *Conclusion*

We found the periods with increased symptoms of depression and anxiety per PHQ-9 and GAD-7 were during initial treatment and in patients with recurrent disease. Patients with metastatic disease also had increased depression symptoms per the PHQ-9. Specific patient- and tumor/treatment-related factors associated with increased symptoms of anxiety and/or depression include use of chemotherapy for treatment, being a woman, tumor in the axial skeleton, and diagnosis of a bone sarcoma. Our study demonstrates that in patients with sarcoma, depression and anxiety exist at a higher prevalence than in the general US population: 15.8% versus 8.6% for depression and 15.7% versus 2.9% for anxiety [11]. When treating patients with sarcoma, potential concomitant psychiatric diagnoses should be recognized and addressed. Screening, especially

at the highest-risk timepoints such as the time of initial diagnosis and the time of recurrence, should be strongly considered. Further work should be done to determine the effect of early psychiatric referral on patient-related outcomes and healthcare costs.

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