

# Anxiety Disorders in Advanced Cancer Patients

## Correlates and Predictors of End-of-Life Outcomes

Ryan Spencer, MD<sup>1</sup>; Matthew Nilsson, BS<sup>2</sup>; Alexi Wright, MD<sup>2,3</sup>; William Pirl, MD<sup>4</sup>; and Holly Prigerson, PhD<sup>2</sup>

**BACKGROUND:** The authors explored associations between anxiety disorders and advanced cancer patients' physical performance status, physician-patient relationships, end-of-life (EOL) treatment preferences and outcomes, and quality of death. **METHODS:** The Coping with Cancer study was a National Cancer Institute/National Institute of Mental Health-sponsored, prospective, longitudinal, multicenter cohort study of patients with advanced cancer. Six hundred thirty-five patients completed the anxiety disorders module of the Structured Clinical Interview for the Diagnostic Statistical Manual IV. The results were compared with patients' baseline physical performance status, treatment preferences, perceptions of the physician-patient relationship, and advance care planning (ACP). **RESULTS:** Approximately 7.6% of patients met criteria for an anxiety disorder. Patients who were diagnosed with an anxiety disorder were more likely to be women and younger and to have a worse physical performance status. Although there were no significant differences in patients' EOL treatment preferences or care, ACP, hospice enrollment, or patients' location of death, there were significant differences in how patients with anxiety disorders perceived the physician-patient relationship. Patients with anxiety disorders had less trust in their physicians, felt less comfortable asking questions about their health, and felt less likely to understand the clinical information that their physicians presented. They also were more likely to believe that their physicians would offer them futile therapies and would not adequately control their symptoms. **CONCLUSIONS:** Women, patients who were more physically impaired, and younger patients with advanced cancer were more likely to meet criteria for an anxiety disorder. Patients with advanced cancer who had an anxiety disorder were more likely to experience greater challenges to the physician-patient relationship. *Cancer* 2010;116:1810-9. © 2010 American Cancer Society.

**KEYWORDS:** anxiety, anxiety disorders, end of life, palliative care, physician-patient relationship, neoplasm.

Although depression has been the focus of most psycho-oncology research, symptoms of anxiety and anxiety disorders have received less attention. Multiple reports cite an incidence of anxiety in this patient population between 6% and 34%,<sup>1-7</sup> and at least 1 study reported an incidence as high as 49%.<sup>8</sup> One study using the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual-IV (DSM-IV) indicated that 4.8% of patients with advanced cancer meet criteria for generalized anxiety disorder (GAD).<sup>9</sup> This is notably higher than the incidence of GAD (3.1%) reported in the general population.<sup>10</sup>

In patients with advanced cancer, the end of life (EOL) is a period when the cancer no longer can be controlled, and the goals of care focus on making patients comfortable and treating their symptoms.<sup>11</sup> Psychological disturbances, including anxiety disorders, adversely affect patients at the EOL. At a time when many wish to be engaged emotionally with loved ones, these disturbances decrease patients' emotional, social, and cognitive function.<sup>1</sup> The capacity of patients for pleasure, meaning, and connection erodes.<sup>12</sup> In addition, mental disorders are a major contributor to diminished quality of life.<sup>13</sup> Anxiety is expected to affect psychological and physical health and also may undermine interpersonal relationships with family, friends, and formal and informal caregivers.<sup>14</sup> Although much attention has been devoted to patient

**Corresponding author:** Ryan Spencer, MD, Department of Obstetrics, Gynecology, and Reproductive Medicine, Brigham and Women's Hospital, 75 Francis Street, ASB-3, Boston, MA 02115; Fax: (617) 730-2833; rjspencer@partners.org

<sup>1</sup>Department of Obstetrics, Gynecology, and Reproductive Medicine, Brigham and Women's Hospital, Boston, Massachusetts; <sup>2</sup>Center for Psycho-Oncology and Palliative Care Research, Dana-Farber Cancer Institute, Boston, Massachusetts; <sup>3</sup>Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; <sup>4</sup>Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

**DOI:** 10.1002/cncr.24954, **Received:** June 11, 2009; **Revised:** July 31, 2009; **Accepted:** August 5, 2009, **Published online** February 26, 2010 in Wiley InterScience (www.interscience.wiley.com)

quality of life at the EOL and interventions to improve it, few studies have examined the associations between anxiety disorders and the physician-patient relationship, patients' performance status, and quality of life near death.

The physician-patient relationship has been regarded as critical to patient care in medical writings, philosophy, and practice—both ancient and modern. Especially in oncology, a trusting physician-patient relationship may help minimize patient shame, humiliation, and power imbalance and can increase the patient's perception that the physician acknowledges and appreciates his or her suffering.<sup>15</sup> It has been posited that a patient afflicted with anxiety will not clearly process information received in a clinical encounter, thereby leading to a communication breakdown that decreases the patient's ability to engage in meaningful dialogue regarding treatment planning, rationale, alternatives, and concerns.<sup>16</sup>

The primary objective of the current study was to examine the associations between anxiety disorders and advanced cancer patients' relationships with their physician, physical performance status, treatment preferences, EOL medical care, and quality of life near death. We hypothesized that advanced cancer patients with anxiety disorders would be more likely to report a lower physical performance status, choose aggressive interventions at the EOL, and have a poorer quality of life near death. We also expected patients with anxiety disorders to have greater difficulties in their perception of the physician-patient relationship.

## MATERIALS AND METHODS

### **Data Collection**

The Coping with Cancer study was a prospective, longitudinal, multisite study of advanced cancer patients and their primary caregivers that was conducted between 2002 and 2008. Patients were recruited from 8 institutions: the Yale Cancer Center (New Haven, Conn), the Veterans Affairs Connecticut Healthcare System Comprehensive Cancer Clinics (West Haven, Conn), Memorial Sloan-Kettering Cancer Center (New York, NY), Simmons Comprehensive Cancer Center (Dallas, Tex), Parkland Hospital (Dallas, Tex), Massachusetts General Hospital (Boston, Mass), Dana-Farber Cancer Institute (Boston, Mass), and New Hampshire Oncology-Hematology (Hookset, NH).

Enrollment eligibility included: 1) a diagnosis of advanced cancer (defined by the presence of distant metastases); 2) a diagnosis at 1 of the participating institutions; 3) age  $\geq 20$  years; 4) patient-identified, unpaid, informal caregiver; 5) ability to complete the interview; and 6) abil-

ity to speak English or Spanish. The institutional review boards on research involving human subjects at each institution approved all aspects of the study design, and each participant offered voluntary, written informed consent.

Each patient and caregiver that enrolled participated in a baseline interview and was compensated with \$25. The interviews were conducted by assistants who were trained by Yale University research staff. To ensure appropriate administration of the DSM-IV SCID, the study assistants needed to demonstrate concordance with the Yale training director's diagnoses ( $\kappa > 0.85$ ). Interviews were conducted in English or Spanish and took approximately 45 minutes to complete. The patients' charts were reviewed to confirm patient demographics and disease characteristics. Within 2 weeks of each patient's death, the caregiver most involved in the patient's last week of life was contacted to review information related to the patient's care and quality of death. Participants were asked to report sex, race, marital status, age at time of interview, educational level achieved, average annual income, treatment center, type of cancer, and religious affiliation as shown in Table 1.

The DSM-IV SCID Axis I Modules were used to diagnose GAD, panic disorder (PD), and post-traumatic stress disorder (PTSD).<sup>17</sup> Patients who screened positive for a particular disorder then completed the full corresponding SCID module. The reliability for the SCID has been demonstrated elsewhere.<sup>18</sup>

An assessment of the patient's perception of their physician-patient relationship was made using a series of questions that are listed in Table 2. A binary response format (ie, yes or no) was used for all of the questions except for the final 2 questions, which assessed the patient's level of comfort in asking about their health and the care that they received. These questions used a Likert scale from 1 (very uncomfortable) to 5 (very comfortable).

To assess the patient's level of terminal illness acknowledgment, the patient was asked: "How would you describe your current health status?" Of 4 possible responses, patients were considered capable of acknowledging the terminal nature of their illness if they responded either with "seriously and terminally ill" or "relatively healthy and terminally ill."

Patients' physical performance status was assessed with the Karnofsky performance scale. This tool, which has demonstrated the ability to predict survival, rates a patient's ability to conduct activities of daily life on a continuum in which 0 represents death and 100 signifies perfect health.<sup>19,20</sup> Comorbid illnesses were determined by

**Table 1.** Characteristics of the Sample of Patients With Advanced Cancer

| Attribute                               | Total Sample  | No. of Patients (%)             |                                    | Comparative Test (Student <i>t</i> Test or Chi-Square Test) <i>P</i> <sup>a</sup> |
|-----------------------------------------|---------------|---------------------------------|------------------------------------|-----------------------------------------------------------------------------------|
|                                         |               | Patients With Anxiety Disorders | Patients Without Anxiety Disorders |                                                                                   |
| No. of patients                         | 635           | 48 (7.6)                        | 587 (92.4)                         |                                                                                   |
| <b>Sex</b>                              |               |                                 |                                    | .006 <sup>b</sup>                                                                 |
| Women                                   | 316 (49.8)    | 31 (64.6)                       | 285 (48.6)                         |                                                                                   |
| Men                                     | 319 (50.2)    | 17 (35.4)                       | 302 (51.5)                         |                                                                                   |
| <b>Race/ethnicity<sup>c</sup></b>       |               |                                 |                                    | .82                                                                               |
| White, non-Hispanic                     | 452 (71.2)    | 35 (72.9)                       | 417 (71)                           |                                                                                   |
| Black, non-Hispanic                     | 94 (14.8)     | 7 (14.6)                        | 87 (14.8)                          |                                                                                   |
| Hispanic                                | 77 (12.1)     | 5 (10.4)                        | 72 (12.3)                          |                                                                                   |
| Asian                                   | 10 (1.6)      | 1 (2.1)                         | 9 (1.5)                            |                                                                                   |
| Other                                   | 2 (0.3)       | 0 (0)                           | 2 (0.3)                            |                                                                                   |
| <b>Married</b>                          |               |                                 |                                    |                                                                                   |
| Yes                                     | 377 (62.4)    | 33 (71.7)                       | 344 (61.7)                         |                                                                                   |
| No                                      | 227 (37.6)    | 13 (28.3)                       | 214 (38.4)                         |                                                                                   |
| <b>Age at evaluation, y</b>             |               |                                 |                                    | .03 <sup>b</sup>                                                                  |
| Mean±SD                                 | 59.70 ± 13.09 | 54.60 ± 13.43                   | 60.11 ± 12.98)                     |                                                                                   |
| Median [range]                          | 60 [22-93]    | 56 [28-78]                      | 60 [22-93]                         |                                                                                   |
| <b>Education, y</b>                     |               |                                 |                                    | .88                                                                               |
| Mean ± SD                               | 12.89 ± 3.95  | 12.81 ± 4.01                    | 12.89 ± 3.95                       |                                                                                   |
| Median [range]                          | 12 [0-24]     | 12 [0-20]                       | 12 [0-24]                          |                                                                                   |
| <b>Income<sup>c</sup></b>               |               |                                 |                                    | .41                                                                               |
| <\$31,000                               |               | 16 (51.6)                       | 179 (41.2)                         |                                                                                   |
| ≥\$31,000                               |               | 15 (48.4)                       | 256 (58.9)                         |                                                                                   |
| <b>Treatment center<sup>c</sup></b>     |               |                                 |                                    | .41                                                                               |
| Yale Cancer Center                      | 152 (24.1)    | 15 (31.3)                       | 137 (23.5)                         |                                                                                   |
| VA                                      | 22 (3.5)      | 2 (4.2)                         | 20 (3.4)                           |                                                                                   |
| Simmons                                 | 55 (8.7)      | 1 (2.1)                         | 54 (9.3)                           |                                                                                   |
| Parkland                                | 191 (30.2)    | 12 (25)                         | 179 (30.7)                         |                                                                                   |
| DFCI                                    | 43 (6.8)      | 2 (4.2)                         | 41 (7)                             |                                                                                   |
| NHOH                                    | 159 (25.2)    | 16 (33.3)                       | 143 (24.5)                         |                                                                                   |
| Other                                   | 10 (1.6)      | 0 (0)                           | 10 (1.7)                           |                                                                                   |
| <b>Cancer site<sup>c</sup></b>          |               |                                 |                                    | .96                                                                               |
| Lung                                    | 147 (23.4)    | 12 (25)                         | 135 (23.3)                         |                                                                                   |
| Colon                                   | 76 (12.1)     | 7 (14.6)                        | 69 (11.9)                          |                                                                                   |
| Pancreatic                              | 50 (8)        | 3 (6.3)                         | 47 (8.1)                           |                                                                                   |
| Breast cancer                           | 76 (12.1)     | 6 (12.5)                        | 70 (12.1)                          |                                                                                   |
| Other                                   | 279 (44.4)    | 20 (41.7)                       | 259 (44.7)                         |                                                                                   |
| <b>Insurance status<sup>c</sup></b>     |               |                                 |                                    | .92                                                                               |
| Insured                                 | 436 (69.9)    | 33 (71.7)                       | 403 (69.7)                         |                                                                                   |
| Uninsured                               | 188 (30.1)    | 13 (28.3)                       | 175 (30.3)                         |                                                                                   |
| <b>Religion</b>                         |               |                                 |                                    | .98                                                                               |
| Catholic                                | 266 (41.9)    | 22 (45.8)                       | 244 (41.6)                         |                                                                                   |
| Protestant                              | 122 (19.2)    | 9 (18.8)                        | 113 (19.3)                         |                                                                                   |
| Baptist                                 | 75 (11.8)     | 7 (14.6)                        | 68 (11.6)                          |                                                                                   |
| Jewish                                  | 17 (2.7)      | 0 (0)                           | 17 (2.9)                           |                                                                                   |
| Other                                   | 118 (18.6)    | 7 (14.6)                        | 111 (18.9)                         |                                                                                   |
| None                                    | 37 (5.8)      | 3 (6.3)                         | 34 (5.8)                           |                                                                                   |
| <b>Patient physical health, mean±SD</b> |               |                                 |                                    |                                                                                   |
| Charlson comorbidity                    | 8.28 ± 2.75   | 8.49 ± 3.31                     | 8.26 ± 2.70                        | .63                                                                               |
| Karnofsky performance status            | 68.40 ± 16.47 | 61.22 ± 20.27                   | 68.97 ± 16.01                      | .01 <sup>b</sup>                                                                  |

SD indicates standard deviation; VA, Veterans Administration; NHOH, New Hampshire Oncology-Hematology; DFCI, Dana Farber Cancer Institute.

<sup>a</sup>Cochran-Mantel-Haenszel statistics.<sup>b</sup>These *P* values represent significant differences between patients with and without anxiety disorders.<sup>c</sup>Missing responses included: marriage (31 patients), income (222 patients), treatment center (3 patients), cancer site (7 patients), and insurance status (11 patients).

**Table 2.** Questions Regarding Physician-Patient Relationships Associated With Advanced Cancer Patients With Anxiety Disorders

| Measure                                                                                                                                                    | Full Sample,<br>N=635 | No. of Patients (%)                            |                                                      | Unadjusted<br>Analyses |                   | Adjusted<br>Analyses <sup>a</sup> |                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------------|------------------------------------------------------|------------------------|-------------------|-----------------------------------|--------------------|
|                                                                                                                                                            |                       | Patients<br>With Anxiety<br>Disorders,<br>N=48 | Patients<br>Without<br>Anxiety<br>Disorders<br>N=587 | OR                     | P                 | OR                                | P                  |
| 1. Do you think doctors here see you as a whole person?                                                                                                    | 560 (89.3)            | 36 (76.6)                                      | 524 (90.3)                                           | 0.35                   | .005 <sup>b</sup> | 0.24                              | .0003 <sup>b</sup> |
| 2. Do you think your doctors here treat you with respect?                                                                                                  | 622 (98.6)            | 47 (97.9)                                      | 575 (98.3)                                           | 0.65                   | .691              | 0.50                              | .5244              |
| 3. Do you respect your doctors here?                                                                                                                       | 627 (99.2)            | 47 (97.9)                                      | 580 (99.3)                                           | 0.32                   | .318              | 0.20                              | .1694              |
| 4. Do you understand most of what your doctor explains to you?                                                                                             | 594 (93.8)            | 41 (85.4)                                      | 553 (94.5)                                           | 0.34                   | .016 <sup>b</sup> | 0.35                              | .0351 <sup>b</sup> |
| 5. Are there things about your health or treatments that you do not understand but want to know about?                                                     | 196 (31.1)            | 20 (42.6)                                      | 176 (30.1)                                           | 1.72                   | .080              | 1.70                              | .1037              |
| 6. If your doctor knew how long you had left to live, would you want him or her to tell you?                                                               | 448 (71.5)            | 33 (68.8)                                      | 415 (71.5)                                           | 0.87                   | .667              | 0.84                              | .6025              |
| 7. Do you believe in taking the medicines your doctor gives you?                                                                                           | 620 (98.3)            | 45 (97.8)                                      | 575 (98.3)                                           | 0.78                   | .817              | 0.77                              | .8097              |
| 8. Do you trust your doctors here?                                                                                                                         | 617 (98.3)            | 43 (91.5)                                      | 574 (98.8)                                           | 0.13                   | .002 <sup>b</sup> | 0.14                              | .0081 <sup>b</sup> |
| 9. Do you think your doctor would offer you treatment that you are told would not help you just because he thought you wanted it?                          | 51 (8.1)              | 10 (20.8)                                      | 41 (7.1)                                             | 3.47                   | .002 <sup>b</sup> | 3.78                              | .0017 <sup>b</sup> |
| 10. Do you think your doctor would offer you treatment that would not help you but would help others with the information its effect on you would provide? | 168 (27.3)            | 12 (26.1)                                      | 156 (27.4)                                           | 0.94                   | .851              | 1.08                              | .8285              |
| 11. Do you think your doctors do a good job of making you comfortable, like controlling your pain?                                                         | 607 (96.7)            | 44 (91.7)                                      | 563 (97.1)                                           | 0.33                   | .056 <sup>b</sup> | 0.30                              | .046 <sup>b</sup>  |
|                                                                                                                                                            | Mean±SD <sup>c</sup>  |                                                |                                                      |                        |                   |                                   |                    |
| Measure                                                                                                                                                    | Full Sample,<br>N=635 | Patients With<br>Anxiety<br>Disorders,<br>N=48 | Patients Without<br>Anxiety<br>Disorders<br>N=587    | β                      | P                 | β                                 | P                  |
| 12. How comfortable are you asking your doctor questions about your health?                                                                                | 4.59 ± 0.91           | 4.29 ± 1.11                                    | 4.62 ± 0.88                                          | −0.10                  | .016 <sup>b</sup> | −0.11                             | .0085 <sup>b</sup> |
| 13. How comfortable are you asking your doctor questions about your care?                                                                                  | 4.60 ± 0.90           | 4.38 ± 1.06                                    | 4.62 ± 0.88                                          | −0.07                  | .071              | −0.07                             | .0738              |

OR indicates odds ratio.

<sup>a</sup>Adjusted analyses were controlled for age, sex, and Karnofsky performance score. Missing data include: Item 1 (8 patients), Item 2 (4 patients), Item 3 (3 patients), Item 4 (2 patients), Item 5 (4 patients), Item 6 (8 patients), Item 7 (4 patients), Item 8 (7 patients), Item 9 (6 patients), Item 10 (19 patients), Item 11 (7 patients), Item 12 (7 patients), Item 13 (0 patients).<sup>b</sup>These P values represent significant differences between patients with and without anxiety disorders (item numbers were added post hoc).<sup>c</sup>Answer choices for Items 12 and 13 ranged from 1 (very uncomfortable) to 5 (very comfortable). Answer choices to all other questions were in a binary yes/no format.

using the Charlson comorbidity index, an age-adjusted measure of chronic illness in which higher numbers signify greater severity of illness.<sup>21</sup>

A postmortem interview with the patient's primary caregiver was performed within 2 weeks after the patient's death. Physical distress, psychological distress, and overall quality of the last week of life were rated. Responses ranged from 0 (least desirable) to 10 (most desirable) with a sum total score of up to 30 to assess the "quality of death." A combination of the caregiver interview and the patient's medical record was used to document the location of death, hospice enrollment, intensive care unit admission, chemotherapy administration, mechanical ventilation, and cardiopulmonary resuscitation.

Information regarding advance care planning (ACP) was obtained from answers to questions posed to patients about do not resuscitate (DNR) order completion, creating a living will, or designating a healthcare durable power of attorney. Participants also were asked about their EOL care preferences regarding the use of chemotherapy, antibiotics, feeding tubes, and ventilators near death.

### Statistical Analysis

Comparative tests were performed to examine whether there were significant differences in the sociodemographic variables of patients who met diagnostic criteria for an anxiety disorder (ie, GAD, PD, or PTSD) from the DSM-IV SCID modules and patients who did not. Student *t* tests were used to assess continuous variables, and chi-square and Fisher exact test statistics were used to assess binary variables. Multivariate logistic regression models were used to examine associations between anxiety disorders and the physician-patient relationship, performance status, terminal illness acknowledgment, EOL treatment preferences, ACP, EOL medical care, receipt of hospice services, location of death, and quality of life near death. *P* values <.05 were considered statistically significant. Criteria for adjusted analyses were used to control for confounders that were associated significantly with both the predictor and the outcome at a *P* value <.10 (Table 1). Potential confounders were age, sex, and Karnofsky performance status; therefore, these variables were controlled for in all analyses. Statistical analyses were performed with SAS statistical software (version 9.1; SAS Institute, Inc, Cary, NC).

### RESULTS

Table 1 indicates that, among 635 patients with advanced cancer in this study, 71.2% self-identified as white,

14.8% self-identified as black, 12.1% self-identified as Hispanic, and 1.6% self-identified as Asian race/ethnicity. Approximately 50.2% of participants were men, and 49.8% were women. Participants had an average of 12.9 years of formal education. Most were married (62.4%) and had health insurance (69.9%). The median time to death in this cohort of patients was 117 days from the time of entrance into the study (not shown in the table).

Overall, 7.6% of patients met SCID criteria for a diagnosis of an anxiety disorder. 3.2% of patients met criteria for PTSD, 3% of patients met criteria for PD, and 3% of patients met criteria for GAD. These patients were 2.3 times more likely (95% confidence interval [95% CI], 1.2-4.1 times more likely) to be women (*P* = .008) and were younger than patients who did not meet criteria for an anxiety disorder (54.60 years vs 60.11 years, respectively; Student *t* test, -2.94; degrees of freedom [df], 703; *P* = .03). There was no association between anxiety disorders and the number of medical comorbidities among patients with advanced cancer, but patients with anxiety disorders had a worse physical performance status (Karnofsky scores of 61.22 vs 68.97, respectively; Student *t* test, -2.61; df, 52.8; *P* = .01).

Table 2 lists the questions that were posed to study participants to assess associations between anxiety disorders and the physician-patient relationship. Patients with anxiety disorders were significantly less likely to trust their physicians (adjusted odds ratio [AOR], 0.14; 95% CI, 0.04-0.47; *P* = .008). When patients were asked whether they believed that physicians would offer treatments that were not helpful just because they thought the patients wanted them, participants with anxiety disorders were more likely to report that physicians would offer futile treatments (AOR, 3.78; 95% CI, 1.61-7.45; *P* = .0017). They also were less likely to report that they understood most of what their physician explained to them (AOR, 0.35; 95% CI, 0.14-0.82; *P* = .0351), and they felt less comfortable asking their physicians questions about their health than patients without anxiety disorders (*u*, -0.11; *P* = .0085). Advanced cancer patients who had anxiety disorders were less likely to believe that their physicians did a good job of making them feel comfortable, including controlling their pain (AOR, 0.302; 95% CI, 0.093-0.982; *P* = .047), or to believe that their physicians viewed them as a "whole person" (AOR, 0.24; 95% CI, 0.11-0.52; *P* = .008).

The diagnosis of an anxiety disorder was not associated significantly with patients' awareness of their terminal illness, the likelihood that they would have ACP in

**Table 3.** Baseline Characteristics Associated With Advanced Cancer Patient Having Anxiety Disorders

| Measure                                                  | Full Sample,<br>N=635 | No. of Patients (%)                            |                                                       | Unadjusted<br>Analyses |     | Adjusted<br>Analyses <sup>a</sup> |     |
|----------------------------------------------------------|-----------------------|------------------------------------------------|-------------------------------------------------------|------------------------|-----|-----------------------------------|-----|
|                                                          |                       | Patients With<br>Anxiety<br>Disorders,<br>N=48 | Patients<br>Without<br>Anxiety<br>Disorders,<br>N=587 | OR                     | P   | OR                                | P   |
| Treatment with anxiolytics                               | 36 (5.70)             | 5 (10.4)                                       | 31 (5.10)                                             | 2.07                   | .15 | 1.44                              | .53 |
| Terminal illness acknowledgement                         | 204 (34.6)            | 19 (42.2)                                      | 185 (33.9)                                            | 1.42                   | .26 | 1.27                              | .49 |
| <b>Treatment preferences</b>                             |                       |                                                |                                                       |                        |     |                                   |     |
| Preference for chemotherapy                              | 327 (52.6)            | 27 (56.3)                                      | 300 (52.3)                                            | 1.17                   | .60 | 1.18                              | .61 |
| Preference for antibiotics                               | 287 (46.9)            | 23 (47.9)                                      | 264 (46.8)                                            | 1.05                   | .88 | 0.96                              | .89 |
| Preference for feeding tube                              | 216 (36.1)            | 22 (50)                                        | 194 (35)                                              | 1.86                   | .05 | 1.58                              | .18 |
| Preference for respirator                                | 160 (25.6)            | 16 (33.3)                                      | 144 (25)                                              | 1.50                   | .21 | 1.34                              | .40 |
| Preference for any type of<br>advanced treatment         | 448 (71)              | 34 (70.8)                                      | 414 (71)                                              | 0.99                   | .98 | 0.91                              | .78 |
| Extend life versus relieve<br>pain                       | 165 (28.8)            | 17 (40.5)                                      | 148 (27.8)                                            | 1.77                   | .08 | 1.57                              | .21 |
| Heroic measures                                          | 129 (20.8)            | 9 (18.8)                                       | 120 (21)                                              | 0.87                   | .71 | 0.62                              | .26 |
| <b>Advance care planning</b>                             |                       |                                                |                                                       |                        |     |                                   |     |
| DNR                                                      | 242 (38.8)            | 17 (35.4)                                      | 225 (39.1)                                            | 0.86                   | .62 | 0.78                              | .45 |
| Living will                                              | 335 (53.9)            | 22 (45.8)                                      | 313 (54.5)                                            | 0.71                   | .25 | 0.85                              | .62 |
| Health care proxy and/or<br>durable<br>power of attorney | 339 (54.5)            | 24 (50)                                        | 315 (54.9)                                            | 0.82                   | .52 | 0.96                              | .90 |

OR indicates odds ratio; DNR, do not resuscitate.

<sup>a</sup>Adjusted analyses were controlled for age, sex, and Karnofsky performance score. Missing data included anxiolytics (3 patients), terminal illness acknowledgement (45 patients), chemotherapy preference (13 patients), antibiotics preference (23 patients), feeding tube preference (37 patients), respirator preference (11 patients), any aggressive preference (74 patients), life extension (61 patients), heroic measures (16 patients), DNR (11 patients), living will (13 patients), and health care proxy (13 patients).

place at baseline, or their treatment preferences/desire for life-extending measures (Table 3). Although it may seem reasonable to expect that patients with anxiety disorders would be more likely to opt for aggressive care at the EOL, our results indicate that this was not the case. Patients with and without anxiety disorders were just as likely to be able to acknowledge their terminal illness, expressed similar baseline preferences for aggressive EOL measures, and had participated in similar ACP activities at the time of study enrollment. Table 3 also shows that there was no statistically significant difference between rates of pharmacologic therapy prescribed to patients with and without anxiety disorders (AOR, 1.440; 95% CI, 0.464-4.469;  $P = .5284$ ).

In addition, the diagnosis of an anxiety disorder was not associated significantly with advanced cancer patients receipt of aggressive EOL care measures, the likelihood of hospice enrollment at the time of death, or the patient's location of death (Table 4). Although patients with anxiety disorders reported more compromise to their physician-patient relationships, this compromise did not

translate into increased aggressive care at the EOL. By using the postmortem assessment completed by patients' primary caregivers, as described above, we observed that there was a significantly lower quality of life during the last week of life reported for patients who met criteria for an anxiety disorder compared with patients who did not meet such criteria (mean, 5.00 vs 6.39;  $\beta$ ,  $-0.11$ ;  $P = .027$ ). This association was no longer significant, however, when the analysis was adjusted for significant confounders, including age, sex, and Karnofsky performance status.

## DISCUSSION

Perhaps the most intriguing and interesting findings of this report came from the analysis of the effect of anxiety disorders on aspects of the physician-patient relationship. We were unable to locate other studies that addressed how psychological disorders in cancer patients affect trust, patient understanding, and comfort and how they feel their physicians view them and their care. In the current

**Table 4.** End-of-Life Characteristics Associated With Advanced Cancer Patients Having Anxiety Disorders

| Characteristic                  | No. of Patients (%) |                                       |                                           | Unadjusted Analyses |                   | Adjusted Analyses <sup>a</sup> |      |
|---------------------------------|---------------------|---------------------------------------|-------------------------------------------|---------------------|-------------------|--------------------------------|------|
|                                 | Full Sample, N=387  | Patients With Anxiety Disorders, N=23 | Patients Without Anxiety Disorders, N=364 | OR                  | P                 | OR                             | P    |
| <b>EOL treatments</b>           |                     |                                       |                                           |                     |                   |                                |      |
| Ventilator                      | 28 (7.3)            | 4 (17.4)                              | 24 (6.6)                                  | 2.97                | .064              | 2.88                           | .134 |
| Feeding tube                    | 31 (8.1)            | 3 (13.6)                              | 28 (7.8)                                  | 1.88                | .334              | 1.28                           | .757 |
| ICU                             | 39 (10.1)           | 4 (17.4)                              | 35 (9.6)                                  | 1.97                | .240              | 1.65                           | .466 |
| Resuscitation                   | 16 (4.2)            | 2 (8.7)                               | 14 (3.9)                                  | 2.37                | .275              | 2.73                           | .243 |
| <b>Hospice</b>                  |                     |                                       |                                           |                     |                   |                                |      |
| Outpatient hospice              | 247 (63.8)          | 16 (69.6)                             | 231 (63.5)                                | 1.32                | .556              | 1.27                           | .660 |
| Inpatient hospice               | 60 (15.5)           | 4 (17.4)                              | 56 (15.4)                                 | 1.16                | .797              | 1.24                           | .741 |
| <b>Location of death</b>        |                     |                                       |                                           |                     |                   |                                |      |
| ICU                             | 28 (7.2)            | 3 (13)                                | 25 (6.9)                                  | 2.03                | .277              | 1.35                           | .725 |
| Hospital (non-ICU)              | 83 (21.5)           | 4 (17.4)                              | 79 (21.7)                                 | 0.76                | .626              | 1.06                           | .923 |
| Home                            | 212 (54.8)          | 13 (56.5)                             | 199 (54.7)                                | 1.08                | .863              | 1.28                           | .621 |
| Hospice                         | 46 (11.9)           | 2 (8.7)                               | 44 (12.1)                                 | 0.69                | .628              | 0.49                           | .493 |
| Quality of death, mean $\pm$ SD | 6.31 $\pm$ 2.93     | 5.00 $\pm$ 2.39                       | 6.39 $\pm$ 2.94                           | $\beta$ , -0.11     | .027 <sup>b</sup> | $\beta$ , -0.08                | .135 |

OR indicates odds ratio; EOL, end of life; ICU, intensive care unit; SD, standard deviation.

<sup>a</sup>Adjusted analyses were controlled for age, sex, and Karnofsky performance score. Missing data included: ventilator (1 patient), feeding tube (4 patients), ICU (1 patient), resuscitation (2 patients), and quality of death (3 patients).

<sup>b</sup>This P value represents a significant difference between patients with and without dependent children.

study, we observed that patients with advanced cancer who had anxiety disorders had less trust in their physicians, were less comfortable asking questions about their health, and also felt less able to understand the medical information that their physicians shared with them. These patients also were more likely to believe that their physicians would provide futile care and were less likely to believe that their physicians did an adequate job controlling their pain. Finally, they also were less likely to believe that their physicians treated them as a whole person.

The trust that a patient places in his or her physician is the foundation of the therapeutic relationship and is what makes the patient an effective partner and participant in healthcare delivery.<sup>22</sup> It has been demonstrated that trust is 1 of the attributes valued most by patients and is taught from the first day of medical school.<sup>23,24</sup> The relation between anxiety disorders and decreased trust is vitally important, because diminished trust can be a factor in communication breakdown, missing appointments, decreased adherence to therapeutic regimens and recommendations, and an overall sense of dissatisfaction with care.<sup>16,22,25</sup>

In addition, patients with advanced cancer who have anxiety disorders were more likely to report a decreased understanding of physicians' explanations of their health

and care. This is a concern, because patients who believe they are knowledgeable and informed are more likely to adhere to prescribed medication regimens and health-related behavioral modifications.<sup>26</sup> Healthcare providers should be aware that patients who are not adherent to recommendations or those who are not comfortable in discussing and asking questions about their health status and care may be suffering from an anxiety disorder and merit further evaluation.

Another finding that may have significant clinical implications is that advanced cancer patients with anxiety disorders believe that their physicians do a poorer job at making them comfortable, including poorer pain control. The importance of this finding is that the primary treatment strategy for many patients with advanced cancer (ie, those with distant metastases) is pain control and comfort, because a cure is not the therapeutic goal. This finding suggests that the efforts of the oncologist, primary care physician, or palliative care specialist to alleviate pain and provide comfort for these patients could be subverted and further suggests the importance of screening for psychiatric disorders to treat patients appropriately.

It is noteworthy that, although patients with advanced cancer who had anxiety disorders reported increased difficulties with their physician-patient

relationships, this did not lead to an increase in aggressive care measures used at the EOL. This may seem contrary to what we would expect or have experienced in caring for advanced cancer patients, anxious patients, and those with diagnosed/diagnosable anxiety disorders. One explanation is that only 7.6% of the studied patients with advanced cancer met diagnostic criteria for an anxiety disorder. A much greater percentage may have subsyndromal levels of anxiety. Statistical power limitations associated with the relative rarity of anxiety disorders may have inhibited our ability to detect more subtle associations between anxious symptoms and care.

In the current study, we observed that the prevalence of anxiety disorders (ie, GAD, PD, PTSD) among patients with advanced cancer was 7.6%, as mentioned above. Several previous studies reported a wide range of estimates for the incidence of anxiety in cancer patients—from 6% to 34%.<sup>1-7</sup> In our study, we used the SCID to diagnose anxiety disorders. Although this method requires intensive interviews, it is the gold standard for diagnosing psychiatric disorders, unlike other survey instruments that provide estimates by using cutoff scores based on symptoms (eg, the Schedules for Clinical Assessment in Neuropsychiatry, the Hospital Anxiety and Depression Scale, the Composite International Diagnostic Interview, the Monash Interview for Liaison Psychiatry, the Memorial Anxiety Scale for Prostate Cancer, or the Generalized Anxiety Disorder Questionnaire).

We also report here that patients with advanced cancer who are younger and women are more likely to meet diagnostic criteria for an anxiety disorder. These findings differ from earlier findings by Stark and House,<sup>27</sup> who reported that traditional risk factors for anxiety—age, marital status, social class, and education—did not apply to cancer patients. Our results, although novel within the cancer literature, are consistent with studies in outpatient and inpatient settings demonstrating that younger patients and women are at greater risk for anxiety disorders.<sup>28,29</sup> It is likely that a confluence of factors explain why these individuals are at risk for anxiety, including contributions from genetic and heritable traits, perceived external trauma, stress, and distinct neural pathways.<sup>30,31</sup> With the exception of PTSD, which occurs after a traumatic event, anxiety disorders usually present earlier in life, and the peak ages of onset are years before the mostly midlife to late-life diagnoses of cancer.

We also observed that anxiety disorders were associated with lower Karnofsky scores among patients with advanced cancer. Patients with anxiety disorders had

nearly a 10-point difference in their performance status, which is roughly equivalent to the difference between being able to care for oneself (Karnofsky performance status, 70) and having to depend on others for assistance in activities of daily living (Karnofsky performance status, 60). This distinction is not trivial. It marks a difference between a patient who has total independence and 1 who has begun to lose a portion of that independence. The initiation of a loss of independence itself can be detrimental psychologically to both patient and family as well as economically challenging, because increased care either inside or outside of the home often is required.

Although cancer care providers often use giving information and reassurance to these patients as first-line “treatment,” we know that it does not effectively combat the anxiety experienced by patients with advanced cancer—especially as they approach death. Stark et al<sup>32</sup> demonstrated that reassurance may not reduce cancer patients’ anxiety and actually may serve to increase anxiety in the most severely afflicted patients.

Those who care for patients with advanced cancer at the EOL must be attuned to the finding that an anxiety disorder may be undermining the physical, emotional and psychological well being of their patients. Reports continue to indicate that physicians are notoriously poor at recognizing patients with psychiatric morbidity,<sup>33-36</sup> referring them for the appropriate services, or adequately treating the disorder.<sup>9</sup> Our study supports this assertion by demonstrating that patients with advanced cancer who have anxiety disorders are no more likely than patients with advanced cancer who do not have anxiety disorders to receive anxiolytic therapy (Table 3). This suggests a need for clinicians to become better versed in screening for anxiety disorders and making referrals to mental health professionals to provide appropriate treatment.

The development of a screening system for anxiety disorders in cancer patients would be a valuable step forward in helping affected patients while ideally not requiring a burdensome amount of already scarce clinician time and effort. We advocate screening for advanced cancer patients not only to aid in the diagnosis and treatment of those with anxiety disorders but also to distinguish them from patients who have adjustment disorders with anxious features—a more prevalent diagnosis that often is given to patients who have poorly defined distress related to their cancer diagnosis. Effective treatments for anxiety disorders exist, whereas those for adjustment disorders are not well established. The comparisons and intricacies of these 2 distinct diagnoses still need to be investigated within a

population of advanced cancer patients and are important areas of focus for future research.

We are unaware of any published, randomized clinical trials for the treatment of anxiety among patients with advanced cancer. Nevertheless, we can extrapolate from other work suggesting that prompt diagnosis and appropriate treatment of anxiety disorders alleviates patients' suffering along with its associated physical and psychological sequelae.<sup>4,5,36</sup>

The current results were generated from a prospective cohort study of patients with advanced cancer who were assessed at baseline and were followed through death, after which a postmortem assessment was conducted. Future research that examines the effects of the treatment of anxiety in patients with advanced cancer will be needed to demonstrate that anxiety can be reduced effectively in this population and that appropriately treated anxiety in patients with advanced cancer is associated with improvements in physician-patient relationships, quality of life, quality of death.

Although the current study demonstrates how anxiety disorders can be detrimental to the physical, interpersonal, medical, and emotional well being of patients with advanced cancer, it is possible that some additional effects could not be observed because of the relatively low prevalence of anxiety disorders in this population (ie, possible effects on EOL outcomes or EOL care decisions). This sample also may have underestimated the rates of anxiety disorders, because all of the participants were required to have an informal caregiver, which may have excluded patients who had less social support, perhaps because of their anxiety. Our hope is that this work will continue to bring to the forefront the necessity of careful assessment of anxiety disorders in patients with advanced cancer.

To our knowledge, this is the first study demonstrating that anxiety disorders have a detrimental effect on the physician-patient relationship and, by extension, may lead to poorer outcomes for these patients. Oncologists, palliative care specialists, and primary care physicians alike have the opportunity to alleviate at least some of the anxiety and subsequent suffering of the patients with advanced cancer for whom they provide care. To further develop a comprehensive understanding of the effects of anxiety disorders on patients with advanced cancer, the focus of future research should include determining the best approaches to screening, referral, and treatment of anxiety disorders in this population. In addition, future work should explore whether and how patients with anxiety dis-

orders have been treated before their cancer diagnosis, with particular reference to treatment failures, successes, and recurrences.

## CONFLICT OF INTEREST DISCLOSURES

Supported in part by the following grants to Dr. Prigerson: MH63892 from the National Institute of Mental Health and CA 106,370 from the National Cancer Institute, Dana-Farber/Harvard Cancer Center U56CA118641 and P30CA0651 pilot grants, and the Center for Psycho-Oncology and Palliative Care Research at Dana-Farber Cancer Institute.

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