The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma

Casey A. Boyd, MD, MS,[a] Jaime Benarroch-Gampel, MD, MS,[a] Kristin M. Sheffield, PhD,[a] Yimei Han, MS,[a] Yong-Fang Kuo, PhD,[b] *and* **Taylor S. Riall, MD, PhD,[a]** *Galveston, TX*

Background. *Depression has been associated with delayed presentation, inadequate treatment, and poor survival in patients with cancer.*

Methods. *Using Surveillance, Epidemiology and End Results and Medicare linked data (1992–2005), we identified patients with pancreatic adenocarcinoma (*N = *23,745). International Classification of Diseases, 9th edition, Clinical Modification codes were used to evaluate depression during the 3 to 27 months before the diagnosis of cancer. The effect of depression on receipt of therapy and survival was evaluated in univariate and multivariate models.*

Results. *Of patients with pancreatic cancer in our study, 7.9% had a diagnosis of depression (*N = *1,868). Depression was associated with increased age, female sex, white race, single or widowed status, and advanced stage disease (*P < *.0001). In an adjusted model, patients with locoregional disease and depression had 37% lower odds of undergoing surgical resection (odds ratio, 0.63; 95% confidence interval, 0.52–0.76). In patients with locoregional disease, depression was associated with lower 2-year survival (hazard ratio, 1.20; 95% confidence interval, 1.09–1.32). After adjusting for surgical resection, this association was attenuated (hazard ratio, 1.14; 95% confidence interval, 1.04–1.26). In patients who underwent surgical resection, depression was a significant predictor of survival (hazard ratio, 1.34; 95% confidence interval, 1.04–1.73). Patients with distant disease and depression had 21% lower odds of receiving chemotherapy (odds ratio, 0.79; 95% confidence interval, 0.70–0.90). After adjusting for chemotherapy for distant disease, depression was no longer a significant predictor of survival (hazard ratio, 1.03; 95% confidence interval, 0.97–1.09).*

Conclusion. *The decreased survival associated with depression appears to be mediated by a lower likelihood of appropriate treatment in depressed patients. Accurate recognition and treatment of pancreatic cancer patients with depression may improve treatment rates and survival. (Surgery 2012;152:403-13.)*

From the Departments of Surgery,[a] and Medicine,[b] The University of Texas Medical Branch, Galveston, TX

Depression is commonly associated with poor outcomes, increased mortality, and decreased compliance with treatment across a variety of disease processes, including stroke, diabetes, kidney disease, heart disease, and cancer.[1-13] Patients with depression may be more likely to partake in high-risk behaviors, have less social support, and be less likely to adhere to screening guidelines or seek appropriate medical care.[14-18]

In particular, patients with cancer have an increased prevalence of depression. Several studies have shown that patients with cancer have rates of coexisting depression ranging from 25% to 58%.[14,17,19-22] In these studies, the diagnosis of depression was made by a variety of methods, including standard diagnostic criteria from the *Diagnostic and Statistical Manual for Disorders, version 3* (DSM-III), personal interviews, and patient-administered questionnaires.

Coexisting depression has been shown to be associated with poorer short-term outcomes in patients undergoing surgery for colon cancer and decreased survival in breast cancer patients.[16,23] Depression is more common in pancreatic cancer patients than in those with other malignancies, with

Supported by grants from the National Institutes of Health (1K07CA130983-01A1 and T32 DK007639), Cancer Prevention Research Institute of Texas (RP101207), the Center for Comparative Effectiveness and Cancer Research, and the Sealy Center on Aging.

Accepted for publication June 7, 2012.

Reprint requests: Casey A. Boyd, MD, MS, Department of Surgery, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0541. E-mail: caboyd@utmb.edu.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2012.06.010

a prevalence ranging from 33% to 71%.[18,20,22,24] Symptoms of depression, such as pain, fatigue, sleep and memory disturbances, anorexia, and weight loss may overlap with those of cancer, making the diagnosis of depression unclear or delayed.[14,17,20,21]

Pre-existing depression in cancer patients, although studied less often, has been associated with advanced or unstaged disease at presentation, a decreased likelihood of receiving definitive treatment, poor survival, and an increased risk of suicide.[16,18,19,21,25-27] Population-based studies of the prevalence of pre-existing depression in patients with pancreatic cancer and its impact on treatment and survival are lacking. The goal of our study was to use the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) data and linked Medicare claims to evaluate the association between pre-existing depression on stage at diagnosis, treatment, and survival in patients with pancreatic adenocarcinoma.

METHODS

This study was approved by the Institutional Review Board at the University of Texas Medical Branch.

Data source. We used data from the SEER tumor registry and linked Medicare claims data collected by the Center for Medicare and Medicaid Services. Developed by the National Cancer Institute, the SEER program collects information on cancer incidence and survival from population-based cancer registries currently covering approximately 28% of the US population. SEER provides information on patient demographics, primary tumor site, histology, stage of disease, first course of treatment, and survival status.

The Medicare data include all claims for covered health care services, including inpatient and outpatient care, for all Medicare patients. The study included patients ≥67 years and 3 months of age who were diagnosed between 1992 and 2005 and their Medicare claims through 2007.

Patients. Our cohort included patients with a primary diagnosis of adenocarcinoma of the pancreas between 1992 and 2005 and who had Medicare data available for linkage. *International Classification of Disease for Oncology, 3rd edition* (ICD-O-3) morphology codes were used for adenocarcinoma (eg, 8000/3, 8010/3, 8020/3, 8021/3, 8022/3, 8140/3 8141/3, 8211/3, 8230/3, 8500/3, 8521/3, 8050/3, 8260/3, 8441/3, 8450/3, 8453/3, 8470/3, 8471/3, 8472/3, 8473/3, 8480/3, 8481/3, and 8503/3). All SEER regions were included. Because a diagnosis of depression in the 3 to 27 months before the diagnosis of pancreatic cancer was assessed in the Medicare claims data, the eligible subjects were limited to patients who were ≥67 years and 3 months of age at the time of pancreatic cancer diagnosis. Patients must have been enrolled in Medicare Part A and Part B without a health maintenance organization for 27 months before and 24 months after cancer diagnosis or until death. Patients diagnosed at autopsy or by death certificate only were excluded.

Measures. A previous diagnosis of depression for each subject was based on identification of *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9-CM) codes for depression (eg, 296.2, 296.3, 296.5, 296.6, 296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1, and 311) in the 3 to 27 months before the diagnosis of pancreas cancer. These ICD-9-CM codes have previously been used in studies of depression and cancer.[16,28] Our goal was to identify patients with pre-existing depression. Therefore, we did not evaluate for depression in the 3 months immediately before the diagnosis of cancer in order to eliminate patients who may have had depressive symptoms as a manifestation of their pancreatic cancer. Patients diagnosed with depression after the diagnosis of pancreatic cancer were included in the "no depression" group.

The SEER program did not use the American Joint Committee on Cancer (AJCC) tumor, node, metastasis staging for pancreatic cancer before 2004. Therefore, tumor stage was analyzed using SEER historic stage. The SEER historic stages were: (1) localized disease (AJCC 0, IA, or IB), (2) regional disease (AJCC IIA, IIB, or III), or (3) distant disease (AJCC IV). Localized disease was defined as tumor in situ or tumor confined to the pancreas. Regional disease was defined as tumor invading adjacent structures, including the duodenum, bile duct, ampulla of Vater, superior mesenteric vessels, hepatic artery, or locoregional lymph nodes. Distant disease required the presence of distant metastases (liver or lung) or metastases outside of the locoregional nodes. Local and regional disease, as previously described, are evaluated together because of an inherent bias in the SEER staging methodology.[29,30] For many patients with advanced stage and unresected locoregional disease, complete pathologic staging and information about tumor differentiation, lymph node status, and tumor size were not available. For these variables, the percentages are based on the denominator of patients with data available. The criterion standard treatment was defined as curative intent surgical resection (ICD-9-CM procedure codes

52.6, 52.7, 52.51, 52.52, 52.52, and 52.59) with or without adjuvant therapy for locoregional disease and chemotherapy (ICD-9-CM diagnosis codes V58.1, V66.2, and V67.2; ICD-9-CM procedure code 99.25; diagnosis-related group code 410; Healthcare Common Procedure Coding System/ Current Procedural Terminology [CPT] codes 96400–96549, Q0083, Q0084, Q0085, J7150, J2353, J2354, and J9000-J9999; and revenue center codes 0331, 0332, and 0335) for distant and unknown stage disease.

Patient comorbidities were determined from the Medicare carrier claims in the 12 months before the diagnosis of pancreatic cancer. The Charlson comorbidity index was used in all analyses, with patients classified as having 0, 1, 2, or ≥3 comorbidities.[31]

We identified inpatient and outpatient visits to surgeons and medical oncologists that occurred between 1 month before and 6 months after the date of diagnosis. Using the carrier files, visits were identified by the American Medical Association's CPT Evaluation and Management codes for office or other outpatient services and consultations (CPT codes 99201–99205, 99211–99215, and 99241–99245) and hospital inpatient services and consultations (CPT codes 99221–99223, 99231–99236, 99237, 99238, and 99251–99255). We obtained physicians' specialties from Medicare Health Care Financing Administration specialty claims codes. Physician specialties were defined as medical oncologists (specialty codes 83 and 90) and surgeons (specialty codes 02 and 91).

Only the month and year of diagnosis were available in the SEER data. The date of diagnosis was defined as the fifteenth day of the documented diagnosis month. Date of death was defined as Medicare date of death (month, day, and year).

Statistical analysis. Summary statistics were calculated for the entire cohort, including gender, race, marital status, age at diagnosis, tumor size (in centimeters), lymph node status, SEER historic stage (locoregional/distant), and treatment (surgery, chemotherapy, or radiation therapy). Physician visits (surgeon or medical oncologist) were evaluated in the groups of patients with and without depression. Analyses were stratified by SEER historic stage. Depression and nondepression groups were compared in bivariate analyses using a 2-group t test for the continuous variable age, a Wilcoxon rank sum test for tumor size, and the Pearson chi-square test for categorical variables. Logistic regression models were used to determine the odds of presenting with advanced stage disease in depressed and nondepressed patients and the odds of receiving definitive treatment (surgery or visit with a surgeon for locoregional disease, chemotherapy, or visit with medical oncologist for distant disease), controlling for age, gender, race, marital status, SEER region, and comorbidities. A Kaplan–Meier time-to-event analysis was used to examine the difference in unadjusted survival between the depression groups. A Cox proportional hazards model was used to analyze 2-year overall mortality for depression groups, controlling for age, gender, race, marital status, SEER region, comorbidities, chemotherapy status (for distant disease), and resection status (for locoregional disease only). Regression analyses were also stratified by disease stage. An additional analysis looking at the association between the use of chemotherapy and depression on survival was performed for patients with locoregional disease who underwent surgical resection. $P < .05$ was considered statistically significant. Statistical analysis was carried out using SAS software (version 9.2; SAS Institute, Inc, Cary, NC).

RESULTS

Patient demographics. Patient demographics can be found in Table I. The overall cohort included 23,745 patients with a diagnosis of adenocarcinoma of the pancreas. The mean age at diagnosis was 78.2 ± 7.0 years. The majority of patients were female, white, and married. Half of the patients had no comorbidities.

One thousand eight hundred sixty-eight patients (7.9%) had a pre-existing diagnosis of depression during the 3 to 27 months before the diagnosis of cancer. Compared to patients without depression, patients with depression were more likely to be older, female, and white ($P < .0001$ for all). Patients with depression were less likely to be married and more likely to be single or widowed ($P < .0001$). One third of patients with depression had no comorbidities, compared to 52.4% of patients without depression ($P < .0001$). Twenty percent of patients with depression had ≥3 Charlson comorbidities. The patterns were similar when stratified by stage.

Tumor characteristics and treatment. Tumor characteristics and treatment can be seen in Table II. In the overall cohort, 31.9% of patients presented with locoregional disease (N = 7,567) and 68.1% with distant or unstaged disease (N = 16,178). Patients with depression were slightly more likely to present with distant or unstaged disease (71.1% vs 67.9%) and less likely to present with locoregional disease (28.9% vs 32.1%; P = .004) compared to patients without depression.

Table I. Patient demographics

Demographic	*Overall* (N = *23,745*)	*Depression* (N = *1,868*)	*No depression* (N = *21,877*)	P *value*
Age (yrs), mean ± SD	78.2 ± 7.0	79.5 ± 7.0	78.1 ± 7.0	<.0001
Female	13,967 (58.8%)	1,351 (72.3%)	12,616 (57.7%)	<.0001
White	19,668 (82.8%)	1,608 (86.1%)	18,060 (82.6%)	<.0001
Married	11,152 (48.4%)	653 (36.2%)	10,499 (49.5%)	<.0001
No. of comorbidities				<.0001
0	12,087 (50.9%)	628 (33.6%)	11,459 (52.4%)	
1	6,452 (27.2%)	546 (29.2%)	5,906 (27.0%)	
2	2,941 (12.4%)	321 (17.2%)	2,620 (12.0%)	
≥3	2,265 (9.5%)	373 (20.0%)	1,892 (8.6%)	

SD, Standard deviation.

Table II. Tumor characteristics and treatment

Characteristic	*Overall* (N = *23,745*)	*Depression* (N = *1,868*)	*No depression* (N = *21,877*)	P *value*
Stage				.00352
Locoregional	7,567 (31.9%)	540 (28.9%)	7,027 (32.1%)	
Distant	16,178 (68.1%)	1,328 (71.1%)	14,850 (67.9%)	
Locoregional disease*				
Tumor size (cm), mean ± SD	4.0 ± 2.3	3.8 ± 1.8	4.0 ± 2.4	.0788
Positive lymph nodes	1,299 (55.8%)	58 (51.3%)	1,241 (56.0%)	.1675
Surgery	1,793 (23.7%)	81 (15.0%)	1,712 (24.4%)	<.0001
Adjuvant chemoradiation	930 (51.9%)	36 (44.4%)	894 (52.2%)	.1712
Chemoradiation only	2,368 (41.0%)	147 (32.0%)	2,221 (41.8%)	<.0001
Visit with surgeon	3,603 (47.6%)	196 (36.3%)	3,407 (48.5%)	<.0001
Visit with medical oncologist	3,961 (52.3%)	240 (44.4%)	3,721 (53.0%)	<.0001
Distant disease				
Chemotherapy	4,371 (27.0%)	221 (16.6%)	4,150 (27.9%)	<.0001
Visit with medical oncologist	7,416 (45.8%)	501 (37.7%)	6,915 (46.6%)	<.0001

*Includes patients with locoregional disease only for whom information was available.
SD, Standard deviation.

In the cohort of 7,567 patients with locoregional disease, 4,983 (65.9%) had information on tumor size and 2,329 (30.8%) on lymph node status. In patients with available data, the mean tumor size was 4.0 ± 2.3 cm. Fifty-six percent of patients had positive lymph node involvement. In patients with locoregional disease who underwent resection (N = 1,793), 1,602 (89.3%) had lymph node information available and 1,610 (89.8%) and information on tumor size. In resected patients, 52.5% had positive lymph node involvement and the mean tumor size was 3.6 ± 3.1 cm. There were no significant differences between the groups of patients with and without depression with regard to tumor size and lymph node status. Patients with depression and locoregional disease were less likely to see a surgeon (36.3% vs 48.5%; $P < .0001$) or medical oncologist (44.4% vs 53.0%; $P < .0001$) and were less likely to undergo surgical resection compared to patients without depression (15.0% vs 24.4%; $P < .0001$).

In the subgroup of patients with locoregional disease who underwent surgical resection, 52.2% of patients without depression and 44.4% of patients with depression received adjuvant chemoradiation ($P = .1712$).

Compared to patients without pre-existing depression, patients with depression who did not undergo surgical resection were less likely to receive chemoradiation (41.8% vs 32.0%; $P < .0001$).

Similarly, patients with distant disease and depression were less likely to have a visit with a medical oncologist (37.7% vs 46.6%; $P < .0001$) and were less likely to receive chemotherapy compared to patients without depression (16.6% vs 27.9%; $P < .0001$).

Odds of presenting with advanced stage disease. In a logistic regression model adjusting for age, gender, race, marital status, and comorbidities, we evaluated the odds of presenting with distant or

unknown stage disease. Patients with pre-existing depression were 13% more likely to present with distant or unknown stage disease (odds ratio [OR], 1.13; 95% confidence interval [CI], 1.01–1.26; P = .0276). Increasing age, male gender, and widowed status were also associated with increasing odds of presenting with advanced stage disease. The number of comorbidities was not a significant predictor of stage at presentation.

Odds of receiving treatment. In a logistic regression model adjusting for age, gender, race, marital status, SEER region, and comorbidities, we evaluated the odds of: (1) patients with locoregional disease undergoing surgical resection and (2) patients with distant/unknown disease receiving chemotherapy. Patients with depression and locoregional disease had 37% lower odds of undergoing surgical resection compared to patients without depression (OR, 0.63; 95% CI, 0.52–0.76; P < .0001). Increasing age, black race, unmarried or widowed status, and increasing number of comorbidities were associated with decreased odds of undergoing surgical resection (Table III).

Similarly, the odds of receiving chemotherapy were evaluated in patients with distant or unknown stage pancreatic adenocarcinoma using a multivariate model. Patients with depression and distant disease had 21% lower odds of receiving chemotherapy compared to patients without depression (OR, 0.79; 95% CI, 0.70–0.90; P = .0003). Additional factors associated with receipt of chemotherapy in depressed patients with advanced stage pancreatic cancer are shown in Table II.

Survival. The median survival for the overall cohort of patients with pancreatic adenocarcinoma, stratified by depression, is shown in Fig 1. Patients without depression had a median survival of 3.1 months, compared to 2.1 months for patients with depression (P < .0001).

The unadjusted median survival for patients with locoregional disease and depression was 4.1 months. Patients without depression had a median survival of 6.6 months (P < .0001; Fig 2). In a Cox proportional hazards model using age, race, marital status, SEER region, and comorbidities, patients with locoregional disease and depression were 20% more likely to die within 2 years compared to patients without depression (hazard ratio [HR], 1.20; 95% CI, 1.09–1.32; P = .0002; Table IV, model 1). Surgical resection was then added to the model (Table IV, model 2). Controlling for surgical resection slightly attenuated the association between depression and survival (HR, 1.14; 95% CI, 1.04–1.26; P = .006), implying that the observed decrement in survival is partly mediated by failure to receive therapy in depressed patients. These results indicate that approximately 27% of the association between depression and 2-year mortality was mediated by surgical resection. Increasing age, male gender, black race, unmarried or widowed status, and increasing number of comorbidities were also associated with worse survival.

Table III. Odds of receiving definitive treatment in depressed patients with pancreatic cancer, stratified by stage

Characteristic	*Odds ratio (95% CI)*
Locoregional*	
Depression (vs no depression)	0.63 (0.52–0.76)
Age (5-yr increments)	0.91 (0.90–0.92)
Male (vs female)	1.00 (0.89–1.11)
Black race (vs white)	0.57 (0.48–0.69)
Married (vs single)	1.28 (1.10–1.49)
Comorbidities (vs 0)	
1	0.88 (0.79–0.99)
2	0.67 (0.59–0.80)
≥3	0.55 (0.46–0.66)
Distant†	
Depression (vs no depression)	0.79 (0.70–0.90)
Age (5-yr increments)	0.91 (0.90–0.91)
Male (vs female)	0.97 (0.90–1.05)
Black race (vs white)	0.72 (0.64–0.81)
Married (vs single)	1.67 (1.51–1.86)
Comorbidities (vs 0)	
1	0.92 (0.85–1.00)
2	0.82 (0.74–0.92)
≥3	0.56 (0.50–0.63)

*Models the odds of undergoing surgical resection.
†Models the odds of receiving chemotherapy.
CI, Confidence interval.

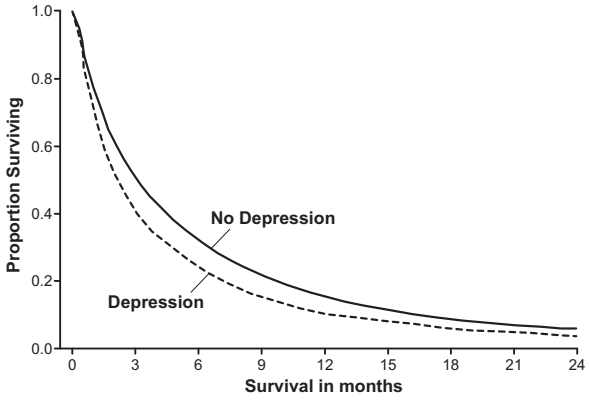

Fig 1. The overall 2-year Kaplan–Meier survival rates of patients with pancreatic adenocarcinoma with and without depression. Patients with depression had a 2-year survival of 3.6% (median survival, 2.1 months) compared to 5.8% (median, 3.1 months) in those without depression.

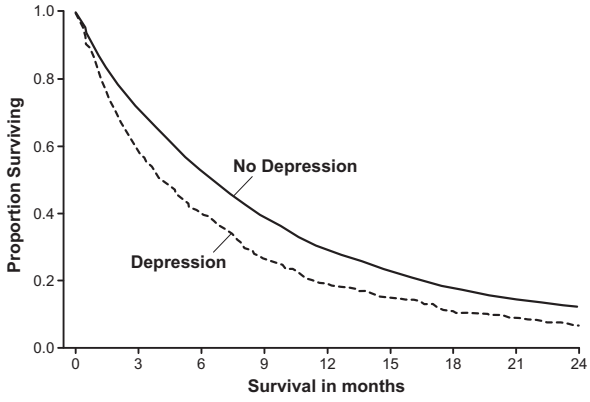

Fig 2. The overall 2-year Kaplan–Meier survival rates of patients with locoregional pancreatic adenocarcinoma with and without depression. Patients with depression had a 2-year survival of 6.7% (median survival, 4.1 months) compared to 12.3% (median, 6.6 months) in those without depression.

A separate analysis was performed for patients with locoregional disease who underwent surgical resection. The median survival of patients with resected locoregional disease without depression was 15.0 months, compared to 10.6 months for patients with depression ($P = .0026$; Fig 3). In the Cox proportional hazards model, increasing age, male gender, black race, ≥2 comorbidities, increasing tumor size, and positive lymph node status were associated with poorer 2-year survival. Pre-existing depression was a significant predictor of survival in patients who underwent surgical resection for locoregional pancreatic cancer (HR, 1.34; 95% CI, 1.04–1.73, $P = .0230$). Adjusting for adjuvant chemotherapy did not significantly change the HR for depression (Table IV, model 2). However, patients who received chemotherapy in addition to surgical resection were 40% less likely to die compared to those who did not receive chemotherapy (HR, 0.60; 95% CI, 0.52–0.68; $P < .0001$).

Fig 4 shows the 2-year survival of patients with distant or unknown stage disease, stratified by depression status. The median survival of patients without depression was 2.2 months, compared to 1.7 months for patients with depression ($P < .0001$). In an adjusted model not including chemotherapy, depression was significantly associated with poorer 2-year survival (HR, 1.08; 95% CI, 1.01–1.14; $P = .0160$). After controlling for receipt of chemotherapy, depression was no longer an independent predictor of survival in patients with metastatic pancreatic cancer (HR, 1.03; 95% CI, 0.97–1.09; $P = .3235$; Table IV, model 2). Approximately 60% of the association between depression and 2-year mortality was mediated by receipt of chemotherapy in patients with distant disease.

Of note, 7.3% of our cohort without depression ($N = 1,727$) had a diagnosis code for depression from 3 months before cancer diagnosis onward. We repeated all analyses with these patients included in the "depression" cohort, in order to consider the possibility that their depression likely existed but went undiagnosed before cancer diagnosis. We also compared the stage at presentation, receipt of surgical resection, and receipt of chemotherapy in the original depression group and the additional depression group. A diagnosis of depression in the 3 months before to any time after the diagnosis of cancer was associated with lower likelihood of advanced stage at diagnosis (OR, 0.86; 95% CI, 0.80–0.93; $P = .0002$), higher rates of surgical resection (35.6% vs 15.0%; $P < .0001$), and chemotherapy (35.9% vs 16.6%; $P < .0001$). Depression at any time point (including the 7.3% diagnosed later) was also associated with decreased odds of dying within 2 years in patients with both locoregional (HR, 0.84; 95% CI, 0.79–0.90; $P < .0001$) and distant disease (HR, 0.87; 95% CI, 0.83–0.91; $P < .0001$).

DISCUSSION

Ours is the first population-based study to examine the association between pre-existing depression and stage at diagnosis, treatment, and survival in patients with adenocarcinoma of the pancreas. Patients with depression were less likely to undergo surgical resection (for locoregional disease), chemotherapy, or radiation, and were less likely to see a surgeon or medical oncologist. Depression was associated with poorer 2-year survival in patients with locoregional disease, but this association was partially attributed to failure to undergo surgical resection in the depressed group. In patients who underwent surgical resection for locoregional disease, there was no difference in the receipt of adjuvant chemotherapy and radiation between depression groups. However, in patients who did not undergo resection for their locoregional disease, depressed patients were less likely to receive chemotherapy and radiation. This may indicate an "all or nothing" trend in the treatment of depressed patients with pancreatic cancer. Likewise, the negative association between depression and long-term survival in patients with advanced stage disease was largely explained by failure to receive chemotherapy.

Our results are consistent with previous studies that revealed that depression is associated with advanced stage at presentation, lower odds of

Table IV. Two-year survival in patients with pancreatic cancer, stratified by stage

	Model 1	*Model 2**
Characteristic	*Hazard ratio (95% CI)*	*Hazard ratio (95% CI)*
Locoregional		
Depression	1.20 (1.09–1.32)	1.14 (1.04–1.26)
Age	1.04 (1.04–1.05)	1.03 (1.02–1.03)
Male	1.07 (1.02–1.13)	1.06 (1.01–1.12)
Black	1.25 (1.14–1.36)	1.13 (1.03–1.23)
Married	0.84 (0.78–0.90)	0.84 (0.78–0.91)
No. of comorbidities		
1	1.00 (0.94–1.06)	0.98 (0.92–1.04)
2	1.25 (1.15–1.35)	1.19 (1.10–1.29)
≥3	1.54 (1.41–1.69)	1.42 (1.30–1.55)
Surgery	—	0.40 (0.37–0.43)
Locoregional plus surgery		
Depression	1.34 (1.04–1.73)	1.32 (1.02–1.70)
Age	1.02 (1.00–1.03)	1.00 (0.99–1.02)
Male	1.22 (1.07–1.38)	1.22 (1.07–1.39)
Black	1.45 (1.13–1.87)	1.35 (1.05–1.73)
Married	1.00 (0.83–1.20)	1.06 (0.88–1.27)
No. of comorbidities		
1	0.96 (0.83–1.10)	0.93 (0.81–1.07)
2	1.25 (1.03–1.52)	1.19 (0.98–1.45)
≥3	1.66 (1.27–2.18)	1.45 (1.11–1.91)
Tumor size	1.01 (1.00–1.01)	1.01 (1.00–1.01)
Lymph node status	1.62 (1.43–1.83)	1.76 (1.55–2.00)
Chemotherapy	—	0.60 (0.52–0.68)
Distant		
Depression	1.08 (1.01–1.14)	1.03 (0.97–1.09)
Age	1.02 (1.02–1.02)	1.00 (1.00–1.01)
Male	1.11 (1.07–1.15)	1.11 (1.07–1.15)
Black	1.01 (0.95–1.07)	0.97 (0.92–1.03)
Married	0.86 (0.82–0.91)	0.95 (0.90–0.99)
No. of comorbidities		
1	1.07 (1.03–1.11)	1.07 (1.03–1.11)
2	1.18 (1.12–1.24)	1.14 (1.09–1.20)
≥3	1.41 (1.33–1.49)	1.30 (1.23–1.37)
Chemotherapy	—	0.49 (0.47–0.51)

*Model 2 incorporates surgical resection (locoregional disease) or chemotherapy (distant disease and resected locoregional disease).

receiving definitive treatment, and poorer survival in patients with a variety of cancer types.[16,19,25,26,28,32,33] In our population-based study, pre-existing depression was a significant predictor of survival in patients with adenocarcinoma of the pancreas. However, after adjusting for receipt of therapy, this association diminished, signifying that the difference in survival in patients with depression is partly mediated by receipt of appropriate therapy for pancreatic cancer. Our results differ from Sheibani-Rad et al,[34] who assessed depression in patients with pancreatic adenocarcinoma in a single-institution study. These authors found no significant difference in stage at presentation or survival between the groups of patients with and without depression.[34] Theoretically, many of the patients in this study had depression before the diagnosis of pancreatic cancer. Patients with a nihilistic attitude toward their disease because of depression (or any other reason) would likely not seek consultation at a specialized center. Therefore, this group of patients may not be representative of the general population of patients with pancreatic cancer and pre-existing depression, because all of them sought care at a tertiary referral center and were more likely to undergo treatment. Because some of the observed survival advantage in our study was mediated by receipt of therapy, it might explain the difference between the current study and theirs. In addition, this study is

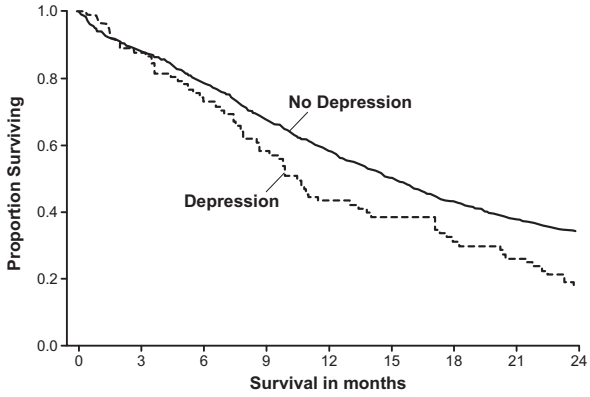

Fig 3. The overall 2-year Kaplan–Meier survival rates of patients with resected locoregional pancreatic adenocarcinoma with and without depression. Patients with depression had a 2-year survival of 17.3% (median survival, 10.6 months) compared to 33.6% (median, 15.0 months) in those without depression.

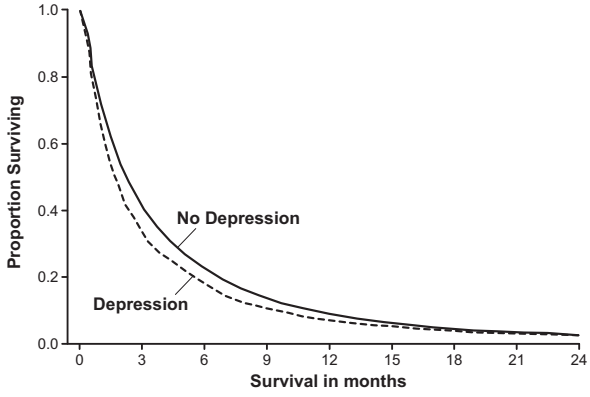

Fig 4. The overall 2-year Kaplan–Meier survival rates of patients with metastatic pancreatic adenocarcinoma with and without depression. Patients with depression had a 2-year survival of 2.4% (median survival, 1.7 months) compared to 2.7% (median, 2.2 months) in those without depression.

limited by a small sample size and may have been underpowered to detect significant differences between depressed and nondepressed patients.

As mentioned above, our study reveals that patients with depression were less likely to see a surgeon or medical oncologist and less likely to undergo surgical resection, radiation, or chemotherapy, and that these disparities in treatment affected long-term survival. Unfortunately, the reasons behind these disparities in treatment (lack of consultation or referral, noncompliance, or not being offered such therapy even after consultation) cannot be elucidated using claims data. Patients with depression may be less compliant with routine health care visits and screening and may be less likely to adhere to medical recommendations, while physicians may be hesitant about providing appropriate care to patients with mental disorders.[28] Our study shows that accurately identifying and treating patients with depression may maximize treatment rates and improve survival and quality of life.

Approximately 8% of patients in our study had a diagnosis of depression before pancreatic cancer diagnosis, which is lower than in previously reported studies but consistent with depression rates in other studies using Medicare claims.[16] In our cohort, 7.3% of patients ($N = 1{,}727$) without depression in the 3 to 27 months before their cancer diagnosis subsequently had a code for depression between 3 months before cancer diagnosis and onward. This rate is lower than would be expected, given that the prevalence of depression in pancreatic cancer patients ranges from 33% to 50% in the literature.[20,22,35] The observed low prevalence in our study is likely related to both undercoding and underrecognition of depression. By using claims data, a diagnosis of depression is only identified when physicians enter a billing code. When treating patients with cancer, identifying, coding, and treating depression may be lower on the list of priorities for physicians, who may feel that treating the cancer is the main concern. Similarly, the symptoms of depression, including fatigue, pain, weight loss, and anorexia, and those of cancer can overlap, making the diagnosis of either difficult.[17,20,21,36-41] Because of this, it is likely that patients with depression went unrecognized and were classified in our study as nondepressed based on billing codes. This would bias our results toward the null hypothesis. However, selection bias may also be affecting our results in the opposite direction. It is possible that only patients with the most severe cases of depression were identified, which would bias our results away from the null hypothesis. We repeated our analyses with the inclusion of the 7.3% of our cohort that was diagnosed with depression from 3 months before cancer diagnosis onward. This analysis indicates that a diagnosis of depression after cancer diagnosis is associated with decreased odds of presenting with advanced stage disease and improved survival. In fact, patients that were diagnosed with depression after cancer diagnosis had higher rates of surgical resection and chemotherapy, supporting our conclusion that the association between depression and survival is mediated by the receipt of appropriate therapy.

Our study shows that depression is a significant predictor of survival in patients with pancreatic adenocarcinoma. Particularly in patients with

distant stage disease, where overall survival is notoriously poor, the impact of depression on survival is small—likely on the order of weeks. The influence of depression in patients with locoregional disease is more pronounced. However, the improvement in survival achieved by accurately recognizing and treating patients with depression is on par with the additional weeks attributed to traditional treatments for pancreatic cancer (surgery and chemotherapy).[42-45] Improving treating physician (surgeon or oncologist) awareness of the high prevalence of depression and appropriate treatment of depression once it is identified can decrease the impact of depression on outcomes in pancreatic and other cancers. Screening for depression can be easily performed by physicians treating patients with pancreatic cancer. Currently, the most cost effective and efficient method is the use of a brief screening questionnaire to identify cancer patients with depressive symptoms, a variety of which are available.[14,19,22,25,32,33,35,38,39,41,46,47] Once identified, patients with depression should be treated with a multidisciplinary approach. Psychiatric or psychological consultation should be sought to optimize the patient's mental health. Physicians specializing in treating pancreatic cancer (oncologists and surgeons) should be aware of the risks associated with pre-existing depression (decreased odds of receiving appropriate treatment, prolonged hospital stay, and decreased survival) and counsel patients appropriately. The treatment of depression is unlikely to have a significant effect on overall survival but might contribute to improved consultation and treatment rates. In addition, screening for depression is simple and inexpensive and treatment may improve quality of life even without survival benefit.[48-50]

Our study has several limitations. We evaluate stage at diagnosis as a surrogate for delay in diagnosis. However, the SEER–Medicare data do not allow us to determine the time from onset of symptoms to definitive diagnosis. In addition, while differences in stage at presentation are statistically significant, they may not be clinically significant. Likewise, only a small proportion of the overall cohort have lymph node or tumor size information. This information was most commonly available in locoregional disease. As such, we do not compare these variables in distant disease and limit our conclusions to those with locoregional disease. Incomplete information available with regard to lymph node status and tumor size may introduce bias. Resected tumors are more likely to have lymph node and stage information, so it is possible that those with missing data represent understaging and actually have worse tumors. Regardless, when the group of patients with locoregional disease is considered together, depressed patients were less likely to see specialists and to receive treatment. In addition, in the group of patients who were resected, depression predicted survival even after controlling for tumor size and nodal status, where the incidence of missing data was low.

Our study population was limited to patients ≥67 years of age and those with Medicare data available for linkage. Given that the mean age at diagnosis is 66 years for patients with pancreatic cancer,[30] the Medicare population is fairly representative of the overall population with pancreatic cancer. We speculate that younger patients with pancreatic cancer, who are not Medicare eligible, would be more likely to have fewer comorbidities, including depression (beacuse depression is more common in older patients), and are therefore more likely to be offered aggressive therapy. In addition, they would be more likely to be married and have greater social support and perhaps more likely to receive such therapy when offered. Our analysis also excludes patients in Medicare health maintenance organizations, because outpatient claims are not available for these patients. Such patients may experience different referral and treatment patterns. Finally, our follow-up is limited to 2 years. It is possible that if we follow our entire cohort for a longer period of time, the association between depression and survival might be mitigated. We repeated our statistical analysis with a restricted cohort of patients with at least 5 years of follow-up (diagnosed between 1992–2002). The patterns were similar to the 2-year survival patients. Depression predicted 5-year survival in patients with locoregional disease, although this effect was no longer significant after adjusting for surgical resection. In patients with resected locoregional disease, depression was not a significant predictor of 5-year survival. This suggests that in patients with resected locoregional disease, tumor characteristics are much stronger predictors of long-term survival. In those with distant disease, 5-year survival is not likely regardless of treatment or comorbidity, so this endpoint is not relevant.

Our study is also subject to selection bias, with patients being more fit for aggressive therapy (surgical resection or chemotherapy) being more likely to be offered such therapy. The improved survival in treated patients, therefore, is likely reflective of both the effect of treatment and the patient's overall status. We have attempted to

adjust for this by including patient age, marital status, and comorbidities in our statistical models, although it is impossible to completely control for selection bias in a study of this type.

In conclusion, this national, population-based study shows that pre-existing depression in patients with pancreatic cancer is associated with advanced stage at diagnosis, decreased likelihood of receiving adequate treatment, and poor survival. Our study indicates that the prevalence of depression in pancreatic cancer patients is lower than expected, which is, at least in part, related under-recognition. Improved vigilance regarding the diagnosis of depression in patients with pancreatic cancer may improve treatment rates and survival. In addition, the treatment of these patients can enhance quality of life in the face of poor survival.

The collection of the California cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the NCI, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should it be inferred. The authors acknowledge the efforts of the Applied Research Program (NCI); the Office of Research, Development and Information (CMS); Information Management Services (IMS), Inc; and the Surveillance, Epidemiology and End Results Program tumor registries in the creation of the SEER–Medicare database.

REFERENCES

1. Himelhoch S, Weller WE, Wu AW, et al. Chronic medical illness, depression, and use of acute medical services among Medicare beneficiaries. Med Care 2004;42:512-21.
2. McCall NT, Parks P, Smith K, et al. The prevalence of major depression or dysthymia among aged Medicare Fee-for-Service beneficiaries. Int J Geriatr Psychiatry 2002;17:557-65.
3. Stordal E, Bjartveit Kruger M, Dahl NH, et al. Depression in relation to age and gender in the general population: the Nord-Trondelag Health Study (HUNT). Acta Psychiatr Scand 2001;104:210-6.
4. Ellis C, Zhao Y, Egede LE. Depression and increased risk of death in adults with stroke. J Psychosom Res 2010;68:545-51.
5. Pan A, Lucas M, Sun Q, et al. Increased mortality risk in women with depression and diabetes mellitus. Arch Gen Psychiatry 2011;68:42-50.
6. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. JAMA 1993;270:1819-25.
7. Kendel F, Gelbrich G, Wirtz M, et al. Predictive relationship between depression and physical functioning after coronary surgery. Arch Intern Med 2010;170:1717-21.
8. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch Intern Med 2000;160:3278-85.
9. de Groot M, Anderson R, Freedland KE, et al. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619-30.
10. Kauhanen M, Korpelainen JT, Hiltunen P, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. Stroke 1999;30:1875-80.
11. Kimmel PL, Peterson RA, Weihs KL, et al. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int 2000; 57:2093-8.
12. Burton HJ, Kline SA, Lindsay RM, et al. The relationship of depression to survival in chronic renal failure. Psychosom Med 1986;48:261-9.
13. Covinsky KE, Kahana E, Chin MH, et al. Depressive symptoms and 3-year mortality in older hospitalized medical patients. Ann Intern Med 1999;130:563-9.
14. Bottomley A. Depression in cancer patients: a literature review. Eur J Cancer Care (Engl) 1998;7:181-91.
15. Chen YH, Lin HC. Increased risk of cancer subsequent to severe depression—A nationwide population-based study. J Affect Disord 2011;131:200-6.
16. Goodwin JS, Zhang DD, Ostir GV. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. J Am Geriatr Soc 2004;52:106-11.
17. McDaniel JS, Musselman DL, Porter MR, et al. Depression in patients with cancer. Diagnosis, biology, and treatment. Arch Gen Psychiatry 1995;52:89-99.
18. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med 2010;40:1797-810.
19. Hinz A, Krauss O, Hauss JP, et al. Anxiety and depression in cancer patients compared with the general population. Eur J Cancer Care (Engl) 2010;19:522-9.
20. Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004;32:57-71.
21. Spoletini I, Gianni W, Repetto L, et al. Depression and cancer: an unexplored and unresolved emergent issue in elderly patients. Crit Rev Oncol Hematol 2008;65:143-55.
22. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19-28.
23. Balentine CJ, Hermosillo-Rodriguez J, Robinson CN, et al. Depression is associated with prolonged and complicated recovery following colorectal surgery. J Gastrointest Surg 2011;15:1712-7.
24. Fazal S, Saif MW. Supportive and palliative care of pancreatic cancer. JOP 2007;8:240-53.
25. Brown KW, Levy AR, Rosberger Z, et al. Psychological distress and cancer survival: a follow-up 10 years after diagnosis. Psychosom Med 2003;65:636-43.

26. Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol 2008;5:466-75.
27. Koroukian SM, Xu F, Beaird H, et al. Complexity of care needs and unstaged cancer in elders: a population-based study. Cancer Detect Prev 2007;31:199-206.
28. Baillargeon J, Kuo YF, Lin YL, et al. Effect of mental disorders on diagnosis, treatment, and survival of older adults with colon cancer. J Am Geriatr Soc 2011;59:1268-73.
29. National Cancer Institute web site. Surveillance, Epidemiology and End Results (SEER) program. Available from: www.seer.cancer.gov. Accessed June 22, 2012.
30. Boyd CA, Benarroch-Gampel J, Sheffield KM, et al. 415 patients with adenosquamous carcinoma of the pancreas: a population-based analysis of prognosis and survival. J Surg Res 2012;174:12-9.
31. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
32. Hamer M, Chida Y, Molloy GJ. Psychological distress and cancer mortality. J Psychosom Res 2009;66:255-8.
33. Steel JL, Geller DA, Gamblin TC, et al. Depression, immunity, and survival in patients with hepatobiliary carcinoma. J Clin Oncol 2007;25:2397-405.
34. Sheibani-Rad S, Velanovich V. Effects of depression on the survival of pancreatic adenocarcinoma. Pancreas 2006;32:58-61.
35. Kelsen DP, Portenoy RK, Thaler HT, et al. Pain and depression in patients with newly diagnosed pancreas cancer. J Clin Oncol 1995;13:748-55.
36. Carney CP, Jones L, Woolson RF, et al. Relationship between depression and pancreatic cancer in the general population. Psychosom Med 2003;65:884-8.
37. Shakin EJ, Holland J. Depression and pancreatic cancer. J Pain Symptom Manage 1988;3:194-8.
38. Patrick DL, Ferketich SL, Frame PS, et al. National Institutes of Health State-of-the-Science Conference Statement: symptom management in cancer: pain, depression, and fatigue, July 15-17, 2002. J Natl Cancer Inst Monogr 2004;32:9-16.
39. Mayr M, Schmid RM. Pancreatic cancer and depression: myth and truth. BMC Cancer 2010;10:569.
40. Fras I, Litin EM, Pearson JS. Comparison of psychiatric symptoms in carcinoma of the pancreas with those in some other intra-abdominal neoplasms. Am J Psychiatry 1967;123:1553-62.
41. Yaskin JC. Nervous symptoms as earliest manifestations of carcinoma of the pancreas. JAMA 1931;96:1664-8.
42. Bilimoria KY, Bentrem DJ, Ko CY, et al. National failure to operate on early stage pancreatic cancer. Ann Surg 2007;246:173-80.
43. Riall TS, Cameron JL, Lillemoe KD, et al. Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. Surgery 2006;140:764-72.
44. Riall TS, Nealon WH, Goodwin JS, et al. Pancreatic cancer in the general population: improvements in survival over the last decade. J Gastrointest Surg 2006;10:1212-23.
45. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006;10:1199-210.
46. Clark KL, Loscalzo M, Trask PC, et al. Psychological distress in patients with pancreatic cancer—an understudied group. Psychooncology 2010;19:1313-20.
47. Holland JC, Korzun AH, Tross S, et al. Comparative psychological disturbance in patients with pancreatic and gastric cancer. Am J Psychiatry 1986;143:982-6.
48. O'Neil A, Sanderson K, Oldenburg B, et al. Impact of depression treatment on mental and physical health-related quality of life of cardiac patients: a meta-analysis. J Cardiopulm Rehabil Prev 2010;31:146-56.
49. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. Int J Psychiatry Med 2006;36:13-34.
50. Rodin G, Lloyd N, Katz M, et al. The treatment of depression in cancer patients: a systematic review. Support Care Cancer 2007;15:123-36.