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DISEASES OF THE ESOPHAGUS

Original article

Psychiatric illness delays diagnosis of esophageal cancer

R. W. O'Rourke, B. S. Diggs, D. H. Spight, J. Robinson, K. A. Elder, J. Andrus, C. R. Thomas, J. G. Hunter, B. A. Jobe

Departments of Surgery and Radiation Medicine, Oregon Health & Science University, Portland, Oregon, USA

SUMMARY. **Evidence suggests that patients with psychiatric illnesses may be more likely to experience a delay in diagnosis of coexisting cancer. The association between psychiatric illness and timely diagnosis and survival in patients with esophageal cancer has not been studied. The specific aim of this retrospective cohort study was to determine the impact of coexisting psychiatric illness on time to diagnosis, disease stage and survival in patients with esophageal cancer. All patients with a diagnosis of esophageal cancer between 1989 and 2003 at the Portland Veteran's Administration hospital were identified by ICD-9 code. One hundred and sixty patients were identified: 52 patients had one or more DSM-IV diagnoses, and 108 patients had no DSM-IV diagnosis. Electronic charts were reviewed beginning from the first recorded encounter for all patients and clinical and demographic data were collected. The association between psychiatric illness and time to diagnosis of esophageal cancer and survival was studied using Cox proportional hazard models. Groups were similar in age, ethnicity, body mass index, and history of tobacco and alcohol use. Psychiatric illness was associated with delayed diagnosis (median time from alarm symptoms to diagnosis 90 days *vs.* 35 days in patients with and without psychiatric illness, respectively, $P < 0.001$) and the presence of advanced disease at the time of diagnosis (37% *vs.* 18% of patients with and without psychiatric illness, respectively, $P = 0.009$). In multivariate analysis, psychiatric illness and depression were independent predictors for delayed diagnosis (hazard ratios 0.605 and 0.622, respectively, hazard ratio < 1 indicating longer time to diagnosis). Dementia was an independent risk factor for worse survival (hazard ratio 2.984). Finally, psychiatric illness was associated with a decreased likelihood of receiving surgical therapy. Psychiatric illness is a risk factor for delayed diagnosis, a diagnosis of advanced cancer, and a lower likelihood of receiving surgical therapy in patients with esophageal cancer. Dementia is associated with worse survival in these patients. These findings emphasize the importance of prompt evaluation of foregut symptoms in patients with psychiatric illness.**

KEY WORDS: **dementia, diagnosis, esophageal cancer, psychiatric illness.**

INTRODUCTION

The incidence of esophageal cancer (EC) has increased by 350% since 1970, and overall 5-year survival is only 10%.[1,2] While the effect of delayed diagnosis on long-term survival in patients with EC is poorly defined, early detection and treatment nevertheless remain the best hope for survival.[3,4] It is therefore important to identify factors that impede timely diagnosis.

Psychiatric illness (PI) is common, affecting close to one-quarter of the US populace.[5,6] Within the Veterans Administration (VA) patient population, the prevalence of PI is even higher and estimated to be greater than 30%.[7] Furthermore, evidence suggests that timely diagnosis and the subsequent management of health problems are impeded by coexisting PI.[8] PI therefore represents a common putative risk factor for delayed diagnosis in patients with EC.

We designed a retrospective cohort study to examine the effect of coexisting PI on diagnosis time-frame and treatment of EC in a VA patient population. The goal of this study is to determine the association between coexisting PI on timely diagnosis and survival in VA patients with EC. Identification of PI as a risk factor for delayed diagnosis of EC provides an opportunity to appropriately modify screening practices in this high-risk and challenging group of patients.

Address correspondence to: Blair A. Jobe, MD, Oregon Health and Science University, Division of General Surgery, 3181 SW Sam Jackson Park Road, L223A, Portland, OR 97239.
Email: jobeb@ohsu.edu

METHODS

Following institutional review board approval, all patients diagnosed with EC from 1989 through 2003 at the Portland Veteran's Administration Hospital were identified by ICD-9 code. Patients with squamous cell carcinoma or adenocarcinoma of the esophagus were included. The cancer diagnosis was confirmed by reviewing the pathology (surgical or endoscopic biopsy) report for each case. Electronic charts were reviewed beginning from the first recorded encounter for all patients.

Demographic data, body mass index (BMI), time from onset of alarm symptoms to diagnosis, survival and EC stage at diagnosis were recorded. Advanced disease was defined as the presence of metastatic involvement (M1a, M1b); regional disease was defined as any cancer of the esophagus without metastatic involvement based on clinical staging. Clinical staging consisted of a chest X-ray, CT scan, and upper endoscopy in most patients. Endoscopic ultrasound was employed in all potential surgical candidates. Bronchoscopy was used to determine whether there was involvement of the membranous airway in surgical candidates. Alarm symptoms for EC included dysphagia, hemorrhage, odynophagia and weight loss. Time to diagnosis was defined as the time from initial estimated duration of symptoms as reported by patients in the initial intake history in the surgical clinic, and verified in accompanying chart notes when possible. DSM-IV diagnoses were made by a psychiatrist or psychologist within the VA system using standard criteria.[9,10]

Statistical methods

Based on normality of data, continuous variables were compared between groups using independent sample *t*-tests or Mann–Whitney *U*-tests. Categorical variables were compared between groups using chi-squared or Fisher's exact test. Univariate comparisons of time to diagnosis and survival data were made using Kaplan-Meier survival curves and log-rank tests. Multivariate analysis of risk factors for time to diagnosis and survival was performed using Cox proportional hazard models to generate hazard ratios (HRs) for the adjusted effect of PI in patients with EC. Hazard ratios are reported with their 95% confidence intervals. A $P < 0.05$ was used to designate statistical significance.

RESULTS

One hundred and sixty patients were identified by the above query and included in the study. Fifty-two patients with EC had one or more DSM-IV diagnoses, and 108 patients with EC had no DSM-IV diagnosis. Patient characteristics are outlined in Table 1. The distribution of specific DSM-IV classification of diagnoses is displayed in Table 2. Seventy-nine percent of subjects in the PI group had major depression. Post-traumatic stress disorder (PTSD), anxiety, dementia, schizophrenia and personality disorders comprised the remaining DSM-IV diagnoses. Of the 52 patients with PI, 18 had multiple DSM-IV diagnoses. The distribution of specific presenting alarm symptoms among all

Table 1 Subject demographics

	N	No psychiatric illness	+ psychiatric illness	*P*-value
Total number of cases	160	108	52	N/A
Age†	159	65.8 ± 10.0	64.6 ± 11.2	0.490
Body mass index†	123	25.0 ± 6.2	24.8 ± 4.5	0.822
Tobacco use‡	134	78 (87%)	40 (91%)	0.579
Alcohol use§	104	41 (60%)	25 (69%)	0.357
Male‡	159	106 (99%)	50 (96%)	0.249
Caucasian ethincity‡	153	102 (98%)	48 (98%)	1.000
Adenocarcinoma/Squamous/HGD§	160	90 (83%)/11 (10%)/7 (7%)	44 (84%)/6 (12%)/2 (4%)	0.779

†Independent sample *t*-test. Values are mean and standard deviation.
‡Fisher's exact test. Values are number of cases and percent within each group.
§Chi-squared test. Values are number of cases and percent within each group.

Table 2 Distribution of specific DSM-IV diagnoses

DSM-IV diagnosis	Cases with any DSM-IV diagnosis ($n = 52$)	Cases with a single DSM-IV diagnosis ($n = 34$)
Depression	41 (79%)	25 (46%)
Post-traumatic stress disorder	10 (19%)	2 (4%)
Anxiety	8 (15%)	3 (6%)
Dementia	7 (13%)	3 (6%)
Schizophrenia	6 (12%)	3 (6%)
Personality disorder	2 (4%)	0 (0%)

Table 3 Clinical outcomes

	N	No psychiatric illness	+ psychiatric illness	*P*-value
Advanced stage disease at diagnosis†	156	19 (18%)	19 (37%)	0.009
Median days from alarm symptoms to EC diagnosis‡	156	35 (0–76)	90 (20–162)	0.001
5-year survival ± S.D.	159	29.6% ± 4.8%	25.0% ± 7.1%	0.525

†Chi-squared test. Values are number of cases and percent within case group and control group.
‡Mann–Whitney *U*-test. Values are medians and interquartile range.
EC, esophageal cancer

patients were: dysphagia in 86%, weight loss in 68%, hemorrhage in 23%, and odynophagia in 18%.

Patients with PI experienced a delay from onset of alarm symptoms to diagnosis of EC compared to patients without PI [medians (interquartile ranges) of 35 days (range 0–76 days) *vs.* 90 days (range 20–162 days], respectively, $P = 0.002$), and more often presented with advanced metastatic disease than those without PI (18% *vs.* 37%, respectively, $P = 0.009$) (Table 3). This delay in diagnosis was not associated with worse long-term survival based on analysis of patient groups with Kaplan-Meier survival curves when all PIs were considered (Fig. 1). The median survival time for patients with PIs was 486 days and 497 days for those without PIs. Five-year survival was also not significantly different, 25.0% versus 29.6% for patients with and without PI, respectively (Table 3, Fig. 1). However, when analyzed individually using univariate Cox proportional hazards models, histology/type of cancer [adenocarcinoma, squamous cell carcinoma, and high grade dysplasia (HGD)] was predictive of both time to diagnosis and survival. In both cases, HGD was significantly different from either carcinoma, but there was no difference between adenocarcinoma and squamous cell carcinoma [survival: HR = 9.635 (1.342–69.17) for adenocarcinoma compared to HGD, HR = 9.261 (1.215–70.596) for squamous cell carcinoma compared to HGD; time to diagnosis: HR = 0.231 (0.108–0.496) for adenocarcinoma compared to HGD, HR = 0.204 (0.084–0.496) for squamous cell carcinoma compared to HGD]. PI was predictive of time to diagnosis but not survival. Age, sex, and the individual DSM-IV diagnoses were also evaluated as predictive factors. Age and dementia were predictive of worse survival while depression was predictive of delayed diagnosis (Fig. 2).

For each outcome variable (survival and time to diagnosis), three multivariate Cox proportional hazard models were created. All models included age and histology/cancer type. The models differed in that one included PI, one included all individual DSM-IV diagnoses, and one included only those individual DSM-IV diagnoses which were significant in univariate analysis. In the three models for survival, only a specific DSM-IV diagnosis of dementia predicted shorter survival time [HR = 2.984 (1.350–6.595)], controlling for age and histology/cancer type. In the three models for time to diagnosis, PI, depression, and a diagnosis of HGD were predictive of delayed diagnosis. In this analysis, a HR < 1 indicates a lower 'hazard' for being diagnosed and therefore a longer time to diagnosis. Hazard ratios for each of these three predictors for delayed diagnosis were: PI, HR = 0.605 (0.424–0.862); depression, HR = 0.622 (0.425–0.910); histology/cancer type, HR = 0.252 (0.117–0.543) for adenocarcinoma compared to HGD, HR = 0.226 (0.093–0.550) for squamous cell carcinoma compared to HGD; age was controlled for in all cases. Patients with HGD

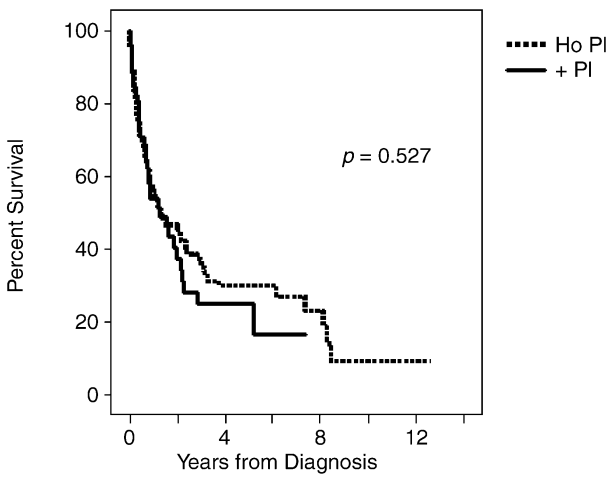

Fig. 1 Kaplan-Meier survival curve comparing patients with psychiatric illness (PI) to those without PI.

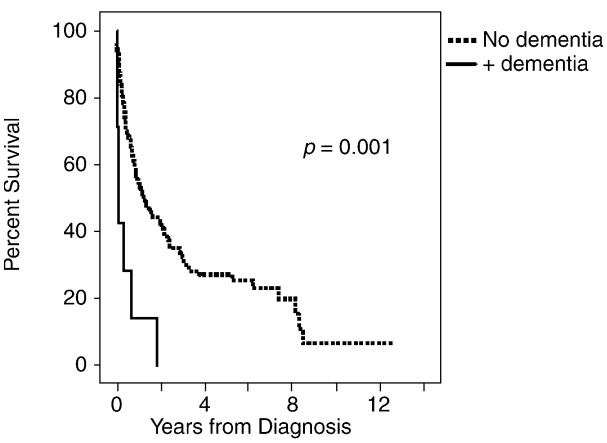

Fig. 2 Kaplan-Meier survival curve comparing patients with dementia to those without dementia.

only comprised 5.6% of this study population ($n = 9$). Elimination of these patients from the ana-lysis did not change the results for any outcome measure.

The association between specific alarm symptoms and outcome measures were also studied in a multivariate model. No single alarm symptom was a significant predictor of time to diagnosis or advanced disease at the time of diagnosis in either univariate Kaplan-Meier analyses or chi-squared analysis. Weight loss and odynophagia were associated with decreased survival in univariate Kaplan-Meier analysis (median survival 208 days with *vs.* 1922 days without weight loss, $P < 0.001$; median survival 261 days with odynophagia *vs.* 588 days without odynophagia, $P = 0.006$)). When analyzed in a multivariate Cox proportional hazard model adjusting for age, histology/type of cancer, cancer stage, neoadjuvant therapy, and each alarm symptom, weight loss (HR = 1.848, 95% CI, 1.013–3.372, $P = 0.045$) and odynophagia (HR = 1.840, 95% CI, 1.035–3.271, $P = 0.038$) remained significant predictors of decreased survival.

Finally, PI was associated with a lower likelihood of receiving surgical therapy: 38% of patients with PI received surgical therapy, compared to 59% of patients without PI ($P = 0.031$, chi-square test). No specific DSM-IV diagnoses were associated with an increased or decreased likelihood of specific therapy, likely due to too few numbers within these subgroups. No differences were observed between subgroups with respect to receipt of neoadjuvant or adjuvant therapy, again likely due to too few numbers within these subgroups.

DISCUSSION

Esophageal cancer is a potentially lethal disease and delay in diagnosis may have a significant impact on survival and other measures of long-term treatment success. It is therefore important to identify risk factors for delayed diagnosis in patients with EC. Despite its high prevalence in the general population, few studies address the role of PI in the timely diagnosis and treatment of cancer in general, and to our knowledge, no previously published data studies this issue in patients with EC. Our data demonstrate that PI in general, a specific DSM-IV diagnosis of depression, and a diagnosis of invasive cancer rather than HGD, are risk factors for delayed diagnosis of EC. Furthermore, PI is a marker for advanced EC at the time of diagnosis, and a specific DSM-IV diagnosis of dementia is associated with worse survival in patients with EC.

Psychiatric illness is common in the general population and influences the diagnosis and treatment of many disease processes.[8] With respect to cancer, it is well-documented that PI delays diagnosis of a number of different types of cancer,[11] but most of the published data addressing this issue are in breast cancer patients.[12,13] The specific DSM-IV class of PI may affect timely diagnosis, although this data is conflicting: one study demonstrated no delay in patients with breast cancer who also had severe mood disorders,[14] while other investigators have shown an increased risk of delayed diagnosis in such patients.[13] Our data support the hypothesis that mood disorders affect timely diagnosis of EC, as depression was associated with delayed diagnosis of EC in our VA patient population. These conflicting findings in the literature are likely explained by differences in study populations and cancer types, as well as other factors in addition to PI that impact on timely diagnosis. An obvious example of such differences in study populations is provided by our VA study group, a patient population with unique demographic and clinical characteristics. Caution must therefore be exercised in extrapolating these findings to the general population.

It is important to ask whether the presence of PI impacts on cancer diagnosis via patient or provider-related factors. One study demonstrated a delay in diagnosis of central nervous system tumors in patients with psychotic symptoms which was exacerbated by a co-existing language barrier.[15] The authors suggest that triage personnel focused on psychiatric complaints to the exclusion of other complaints, confounding diagnosis. Whether a patient's pre-existing psychiatric diagnosis may affect a health care provider's ability to provide expeditious diagnosis and treatment in the absence of a language barrier is unknown. At least one study in patients with breast cancer demonstrated that the presence of psychiatric disorders in patients with cancer does not affect physician compliance with appropriate treatment,[16] suggesting that PI is more likely to affect patient rather than provider-related factors that impact on timely diagnosis and treatment.

The diagnosis of EC in patients with PI is further complicated by the fact that unexplained foregut symptoms including dysphagia, a hallmark symptom of EC, are more common in patients with PI. One study demonstrated dysphagia in one-third of patients with PI, markedly higher than estimates of 6% in the general population.[17,18] Others have also demonstrated an association between PI and unexplained foregut symptoms including reflux-related complaints.[19] O'Malley *et al.* demonstrated that 75% of patients with PI presenting with generalized foregut-related symptoms had normal findings on endoscopy compared with only 20% of patients without PI, highlighting the diagnostic challenges in this patient subgroup.[20] Such symptoms may be primarily psychogenic, or related to psychiatric medications, including antipsychotic and anticholinergic medications.[21]

In addition, diseases of esophageal motility including spastic disorders of the esophagus and non-specific motility disorders, may be associated with a higher prevalence of coexisting PI, although this association is debated.[22] Finally, higher rates of alcohol abuse in patients with mental illness[23] may contribute to alcohol-related esophageal symptoms: alcohol lowers lower esophageal sphincter pressure, which may exacerbate gastroesophageal reflux disease and result in esophageal symptoms. These observations underscore the need for vigilance in the challenging subgroup of patients with coexisting esophageal disease and psychiatric illness.

Our data also suggest that PI may impact on treatment delivered, as PI was associated with a decreased likelihood of receiving surgical therapy. It is not possible to determine from this retrospective chart review whether this association was due to patient refusal or non-compliance, a bias against offering surgery to patients with PI among providers, or a combination of these and other factors. Nevertheless, these findings suggest that PI impacts on delivery of surgical therapy to patients with EC.

Our data demonstrate a survival disadvantage associated with a diagnosis of dementia, while other specific PIs were not associated with worse survival. This may be the result of inadequate study size, especially in light of the large number of patients with major depression and the correspondingly low numbers of patients with other DSM-IV diagnoses in this study group. Alternatively, other unknown clinical factors specific to this VA study population may also impact on diagnosis and survival and mask the association between specific PIs and these measures. For example, follow-up treatment focused on both the PI and EC is facilitated by the comprehensive nature of the VA medical system. Thus, receiving treatment for both conditions may moderate the effects of PI on survival. Despite these study limitations, it is possible that specific DSM-IV diagnoses may have different effects on diagnosis and survival in patients with EC. Further study of larger and more diverse patient populations will be necessary to fully define the association between specific PIs and timely diagnosis and survival in EC. This study is also limited by the biases and confounders associated with restrospective reviews, including the use of patient recall to define duration of symptoms.

This is the first report to study the association between PI and diagnosis and survival in patients with EC. PI is a risk factor for delayed diagnosis of EC and advanced cancer stage at the time of diagnosis, while dementia is associated with worse survival in patients with EC. PI is also associated with a decreased likelihood of receiving surgical therapy. These hypothesis-generating observations emphasize the challenges in diagnosis and treatment of EC in patients with PI, and the importance of prompt evaluation of foregut symptoms in all patient populations. While widespread endoscopic screening of all patients with psychiatric illness and foregut symptoms may not be practical, future therapeutic clinical trials should be designed to study coexisting PI in patients with EC and define better predictors of risk for EC in this challenging patient population. These data suggest the need for education of health care providers of the increased risk of delayed diagnosis of EC in patients with PI, along with institution of proactive symptom interrogation and a lower threshold for diagnostic testing in this high-risk patient population.

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