Introduction

Depression and anxiety are emotional disorders that commonly affect patients with esophageal cancer (1). Esophageal cancer is a highly morbid disease with a 10–15% overall 5-year survival and a 15–40% postoperative survival (2,3). At the time of diagnosis, only 25% of patients are eligible for treatment. When possible, they undergo an extensive course of therapy that can include neoadjuvant chemoradiation followed by surgeries that have a high rate of complications (4–6). As such, this patient population is at particularly high risk for developing or exacerbating affective disorders, even amongst patients with other forms of cancer (7–10). Moreover, psychosocial illness can affect compliance with surveillance and treatment, and ultimately may affect patient outcomes and survival (9–12). This not only affects the individual, but also has the potential to dilute therapeutic data and underestimate the efficacy of modern therapies.

Unfortunately, there is wide variability in both study design and diagnostic criteria that limits our understanding of these disorders and their effects on outcomes.
review will discuss the existing literature on depression and anxiety in esophageal cancer patients, their effects on treatment, compliance, outcomes, and possible interventions that may optimize quality of life.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3529).

Methods
A PubMed search for English-language articles describing affective disorders in the setting of esophageal cancer was conducted from 2000 to 2020. Key words included “anxiety”, “depression”, “esophageal cancer”, “risk factors”, “prevalence”, “treatment” and all appropriate Boolean operators. We prioritized research from randomized trials that investigated the prevalence and incidence of affective disorders, which involved the use of questionnaires, clinical interview, or formal psychiatric evaluation. Non-randomized studies that discussed risk factors, mechanisms, treatment, and future research were also included from case series, retrospective studies and other review articles. The guidelines, original works and foundational studies from professional societies and leaders in the field were also reviewed. Only articles agreed upon by all authors were included.

Discussion

The problem with prevalence

The true prevalence of depression in esophageal cancer patients remains controversial. While clinically relevant psychological distress is commonly accepted to affect about a quarter of cancer patients, reports are highly variable with published ranges anywhere from 5% to 54% (13-17). This is likely due to differences in disease-related characteristics, heterogeneity in study design, culture-bound differences in the perceptions of illness, and the limitations of our measurement tools (7,12-14).

The most troubling of these tools is the Hospital Anxiety and Depression Scale (HADS). First introduced by Zigmond in 1983, the HADS is the most commonly utilized evaluation method in the literature (18). It is a 14-question, patient completed self-assessment that grades the likelihood and severity of depression and anxiety on a scale from 0–21 (19). In the original paper, a patient was asked to fill out a questionnaire, followed by a 20-minute evaluation by a clinician, and a follow up interview with researchers. Zigmond defined scores of 7 or less as “non-cases”, 8–10 as “doubtful cases”, and 11 or more as “definite cases”.

The HADS is widely regarded as a valid and reliable instrument for the detection of psychological distress in cancer patients (14,20-22). As a result, many studies utilize the HADS as their primary means of evaluation; a widespread decision that has three significant vulnerabilities.

First, the HADS was never intended as a diagnostic tool. In a commonly cited study intended to validate the HADS, Mitchell and colleagues write that for “…the identification of depression, anxiety or distress in cancer settings, the HADS (including subscales) is not recommended as a case-finding instrument but it may... be a suitable addition to a screening programme (sic) (18).” As Mitchell and colleagues caution, the incidence of depression is especially unclear because most studies rely only on screening tools instead of formal diagnostic methods (23). Diagnosis has a greater burden of proof, relying on a formal algorithm, a context of clinical significance, and a minimum duration of time (23). The HADS is deficient in all of these qualities. Nevertheless, since the HADS—and similar screening tools—are being utilized to identify new cases of depression, they serve as de facto diagnostic instruments. Worse, such use is commonly regarded as the gold standard for this type of research (1).

Originally, the HADS score was intended to be a rapid screening method for “clinically significant anxiety and depression in patients attending general medical clinics (19).” It was designed to improve upon the already utilized General Health Questionnaire (GHQ), which was developed by Goldberg in 1972 (24). It is described as “rather long” and only “detects a ‘case’ [of psychiatric distress] but gives no information about the nature of the psychiatric disorder (19,24).”

While other studies have shown that HADS may be superior to the GHQ, it is difficult to justify the unsupported use of either screening tool to report reliable prevalence data (25). Härtner in 2006 published one such study that showed the HADS score to be superior to the GHQ (Depression sensitivity 74% vs. 52.5%, specificity 80% vs. 77.9%; Anxiety sensitivity 70.7% vs. 75.6%, specificity 73% vs. 55.9%). However, since the sensitivity and specificity determined by the authors is qualitatively similar to the study by Mitchell in 2010, these findings also do not support the use of the HADS (18,25).

Second, there is no established standard for a positive threshold. Many of the studies referenced in this review use
an 8 on the HADS to diagnose anxiety or depression; some using the standard HADS, and some using the subscales. Unfortunately, Zigmond would classify a score of 8 as “doubtful,” and unsurprisingly, the use of this value has been shown to yield low sensitivity and specificity (14,19).

Third, even when a higher cut-off is used, the HADS does not perform adequately. In a paper by Härter and colleagues, they publish that the best cutoff points for HADS are 17 for any mental disorder or an anxiety disorder, and 18 for depressive disorders (25). For any mental disorder, this corresponds to a sensitivity of 58.8%, specificity of 77.9%, and positive predictive value of 44%. For a depressive disorder, sensitivity is 73.7%, specificity is 79.5%, and positive predictive value is 30.7% (25). Even with this higher threshold, this data suggests substantial limitations in the HADS to establish accurate diagnoses.

Are we using the right definitions?

Complicating matters further, traditional psychiatric definitions of axis I disease may not even be valid in the cancer patient population. Keller and colleagues performed a study in 2004 that compared the HADS to physician and nursing evaluation, and structured clinical interview in cancer patients (14). A total of 186 patients were evaluated by HADS, 181 were rated by medical staff, and 78 consented to formal psychiatric assessment. All 186 patients filled out the HADS questionnaire. Using a threshold of ≥11, 13.9% were found to have depression and 19.1% were found to have anxiety. Interestingly, a value of ≥16 was defined by the authors to be closest to DSM-IV diagnostic criteria. When this standard was applied, 19 of the 22 patients with a current psychiatric disorder were identified (sensitivity 86%), and 48 out of 55 patients without a psychiatric illness were accurately identified as non-cases (specificity 87%). Of those, 181 patients were evaluated by medical staff using a questionnaire created by the authors. Surgeons and nurses taking care of these patients interpreted that 52.7% and 56.9% respectively had symptoms suggestive of a formal DSM-IV diagnosis and 55% and 54.5% were distressed (14). While the correlations between these findings were low—Kappa values range from 0.15 to 0.23—it does raise an important point. If clinicians believe that more patients are suffering emotional distress than those with diagnosable disease, the need for psychosocial support may be broader than we predict. Depression is only one disease in a spectrum of affective disorders, and traditional criteria may not even apply to this patient population. As Mitchell describes, the DSM is “…generic and might not be appropriate in cancer settings (23).”

The virtue of questionnaires

Despite these limitations, the HADS has substantial clinical utility. Whether due to heavy workloads or lack of formal training, oncologic doctors and nurses have been shown to be poor identifiers of psychological distress (11,14,23). In a study performed by Newell in 1998, oncologists’ specificity in detecting clinical anxiety and depression was 17% and 6% (11). However, those same oncologists were able to identify much higher levels of need than patients were initially able to report. This resulted in sensitivity rates of major physical symptoms up to 80% (11). These findings suggest that while oncologists’ knowledge of and relationship with patients resulted in an awareness of physical problems, they were unable to identify psychological distress. In meta-analysis of multiple studies, Lampic and colleagues reported that the correlation between patient and staff perceptions of depression and anxiety ranged from 0.21 to 0.35 (26). However, significant variability amongst studies made interpretation of these findings difficult. Lampic reports that correlations of <0.35 were regarded by some authors as being able to interpret mood states with “some accuracy,” while others interpreted values from 0.31 to 0.50 as clinicians being unable to “accurately determine what the patients felt (26–28).” Unless all patients undergo formal psychiatric evaluation, some form of diagnostic adjunct is necessary to assist with the limitations of untrained clinicians.

The HADS is not the only questionnaire-based evaluation of mental health. The Brief Symptom Inventory (BSI), the Symptom Checklist 90 (SCL-90), the Minnesota Multiphasic Personality Inventory (MMPI), the Beck Depression Inventory (BDI), and the Hamilton Rating Scale for Depression (Ham-D) have all been utilized with comparable utility to the HADS (7). While the prevalence of depression and anxiety vary depending on the screening instrument used, the HADS is most frequently utilized in the literature (29). A full evaluation of each of these methods is beyond the scope of this review.

Unfortunately, there is a paucity of studies that do not rely on a patient-based questionnaire. Singer, noting similar concerns, performed a meta-analysis of studies using a structured clinical interview. With appropriate exclusion criteria and no restrictions on date of publication, Singer
and colleagues found only 8 studies. While none of the papers included esophageal cancer patients, the published rates of depression ranged from 23% among breast cancer patients in Turkey to 53% among elderly patients with unspecified tumor in Uganda (1).

Hu and colleagues in 2014, noting that most studies involve small populations, performed a retrospective analysis of 28,454 patients; 14,227 with esophageal cancer and 14,227 matched for age, sex, common-comorbidity and enrollment date (8). Diagnosis was established by searching discharge diagnosis codes and new prescriptions for anxiety or depression medication, criteria that require formal evaluation by a psychiatrist. They found that of the 28,454 patients, 990 (3.5%) were diagnosed with anxiety and depression disorders: 382 in the esophageal cancer group with a cumulative incidence of 20.1 per 1,000 patient-years, and 608 in the matched cohort 9.2 per 1,000 patient-years (8). While this study is important, we were unable to find another study with reported incidence in the form of patient-years, making comparison difficult.

In 2011, Mitchell performed a meta-analysis on the prevalence of affective disorders on patients in the oncological, hematological and palliative care setting (23). He was able to identify 94 studies (24 in the palliative setting and 70 in the non-palliative setting) for a total pool of 14,078 patients; all of whom were evaluated by clinical interview. He found 16.3% had major depression or a major depressive episode, 14.9% had major depression only, 19.2% had minor depression only, 20.7% had any depression, 31.6% had depression or adjustment disorder, and 38.2% had depression or adjustment disorder or an anxiety disorder (23). While this analysis includes subjects with many forms of disease, these findings still serve as an important touchstone.

Previously cited, the study by Keller and colleagues identified 22 of the 78 (28%) patients who underwent formal psychiatric evaluation of a total group of 186 (14). But this study was not performed exclusively on esophageal cancer patients, and was not designed to investigate incidence.

**Timing**

Adding to the heterogeneity in the literature, studies perform patient evaluations at different times during treatment. Unfortunately, prevalence is known to change over time and increase during critical events: initial diagnosis, the beginning of treatment, evaluation of response to treatment, after recurrence, and during terminal stages (29-31). Patients appear to experience the greatest psychological distress and impairments in quality of life during the first year following diagnosis, but feelings of anxiety and depression may remain elevated for up to 4 years (32-34). Of particular note, Fang and colleagues found that cancer patients are the most vulnerable for the first 3 months after diagnosis, reporting a nearly 16-fold increased risk of suicide compared with cancer-free patients (35,36).

Hellstadius and colleagues investigated the incidence of affective disorders at three stages in esophageal cancer patients: before surgery, 6 months post-surgery, and 12 months postsurgery. Anxiety was present in 33%, 28% and 37% while depression was present in 20%, 27%, and 32% respectively (9). These findings call into question the timing for psychological evaluation and whether studies relying on single time points accurately reflect emotional distress.

**Risk factors**

While the actual prevalence of affective disorders may be unknown, esophageal cancer patients represent an especially high-risk population. Multiple studies have reported that depression and anxiety are significantly higher in esophageal cancer than both the general population and among other forms of cancer (7-10).

In a cohort of 28,454 matched hospitalized patients, Hu and colleagues found that having esophageal cancer increased the risk of new depression by a hazard ratio of 2.24 (8).

Hong in 2014 investigated the prevalence of anxiety and depression in 1,217 Chinese cancer patients using a HADS threshold >11. Compared to a rate of 3.8% in the general population, anxiety and depression among all cancer patient were identified in 6.49% and 66.72% respectively. Among esophageal cancer patients, 75.81% were found to have depression; higher than patients with gastric cancer (63.40%) and the second most frequent overall after lung cancer (77.19%) (13).

There is a large body of work in the literature that has investigated the causes for this observation. Limitations in activity status and reduced quality of life are often central to most risk factors (34,37,38). Unfortunately, the specific causes are presented haphazardly; often described in qualitatively different ways, through quantitatively different variables, and rarely with the standardized weight of hazard.
The diagnosis is traumatic
At the time of diagnosis, most patients will not be surgical candidates. Esophageal cancer carries a 10–15% overall 5-year survival, and a 15–40% postoperative survival (2,3,39). Patients are often diagnosed at a late stage, when only 25% will be eligible for treatment; which places it among the least favorable of all cancers (4-6,8). Due to its poor outcomes, new diagnosis with esophageal cancer has been described as a “death sentence,” and is among the highest risks for causing depression and anxiety (8,34,40–42). It has even been suggested that the experience may evoke symptoms of post-traumatic stress (8,40). As described earlier, the first months to year following diagnosis are the highest risk for depression and suicide, with an up to 16-fold increase compared to the general population (29-31,35,36).

Postoperative complications are common and significantly affect quality of life
Following diagnosis, and when possible, surgery for esophageal cancer is invasive and comprehensive. Treatment often requires large incisions, gastrointestinal reconstruction, and enteral feeding access, and may require neoadjuvant chemoradiation (4,9,43–46). Collectively, the different types of esophagectomy remain some of the highest-risk elective operations, with peri-operative mortality reported from 3% to 20% (45,46). Starting treatment has been shown to decrease rates of anxiety and depression following diagnosis, unless treatment has palliative intent (33).

Rates of in-hospital complications (including wound infection, pneumonia, pneumothorax, Anastomotic leak, and mediastinitis) can be as high as 40–50%, and are known risk factors for depression (9,47). The resulting physical symptoms experienced by patients—pain, inadequate symptom treatment, prolonged hospital stay and limitations in activity status—are also significant risk factors, and may explain this phenomenon better than the complication itself (13,14,23,37,38).

Dysphagia, one of the most common symptoms before diagnosis, is another significant cause of emotional distress (9,48). Unfortunately, even following surgery, more than a third of patients will report persistent dysphagia for up to 5 years (49). In addition to affecting overall quality of life, re-experiencing symptoms that were present before treatment compound the emotional distress of the morbidity alone (9).

Long term complications, including strictures, post-vagotomy syndromes, dumping syndrome, weight changes, limitations in eating habits, and the ever-present risk of recurrence, are also known causes of emotional distress (7,8,42).

Social consequences and returning to normalcy
Even with an uncomplicated therapeutic course, some patients may experience difficulty returning to their normal lives. Many patients describe some form of dysphagia or food intolerance following surgery (49). This results in dietary changes, weight loss, and a recovery process that feels similar to symptoms experienced before treatment (42). Biofeedback mechanisms of satiety, nausea and vomiting often have to be re-learned by patients, which can significantly affect gatherings and day-to-day interaction (42). Enteral Feeding is a routine element of esophagectomy and is also known to be an independent risk factor for developing depression for similar reasons (8,50). The regular use of tube feeds requires bulky equipment, professional care, and formula-based diet. As a result, patients may feel socially isolated, which not only depresses mood, but may reduce support mechanisms, and increase the result of depression and suicidal thoughts (7,8,23,42).

Similarly, patients living alone were more likely to report anxiety than patients who are married or cohabitating. This is likely due to the stress-buffering effect of social support, which has been associated with both lower anxiety and depression in cancer patients (9,51).

Biochemical theories
There is some evidence to suggest that there may be biochemical mechanisms that predispose patients to depression. Cerebrovascular disease, cirrhosis, chronic inflammatory changes, impaired serotonergic neurotransmission, current and former smoking have all been shown to increase the risk of depression in cancer patients (8,38,52–54).

Substance abuse is also higher among survivors of esophageal cancer than both the general population and other forms of cancer (55) In a study from South Korea, 19.4% of patients with psychological distress exhibited some form of substance abuse; 90% of which was alcohol related (55). Since alcohol is a known risk factor for esophageal squamous cell carcinoma, this likely reflects a combination of both pre-existing users and post-diagnosis coping mechanisms (56). Additionally, since cirrhosis also increases the risk of depression, multiple abuse-related factors appear to influence depression in this already high-risk population (52,55). Causative or correlative effects of
substance abuse need to be further explored to determine how best to treat and/or prevent this comorbidity in esophageal cancer survivors.

The presence of metastases has also been associated with anxiety in patients with gastrointestinal cancers, but not breast cancer (7). This suggests that factors specific to cancer biology may play a role instead of the psychology effect of the metastases themselves. (7). For example, a study by Cheng and colleagues found that the mitogen-activated protein kinase molecule, p38, was associated with reduced survival, higher rates of recurrence, lymph node metastases and also depression (57).

On the other hand, Hellstadius and colleagues, in their paper investigating rates of affective disorders over time showed that changes in anxiety were unrelated to tumor recurrence and subsequent treatment. Though they were not able to prove the same about changes in depression, it does suggest that there was no relationship to tumor-related biochemical factors (9).

Though controversial and vulnerable to confounding, these studies reveal that our understanding of cancer-related depression requires further investigation.

Psychiatric factors
Typical research into affective disorders focuses on new cases after diagnosis with esophageal cancer. However, it must be noted that patients with pre-existing anxiety or depression have a higher likelihood of developing the other (38,58). Moreover, patients suffering from both will experience more severe symptoms and less improvement after treatment (7).

Demographic factors
Age, gender, and even education have all been suggested as risk factors for anxiety or depression, but are inconsistent in the literature (8,9,13). Of note, multiple studies have suggested female gender is an independent risk factor for anxiety but not depression (9,14,38,59). To the authors’ knowledge, no study was able to identify a mechanism for this finding, which may simply reflect an increased willingness to communicate.

Effects on outcomes
In addition to decreasing overall quality of life, depression is known to exert physical consequences on cancer patients. While the mechanisms remain elusive, multiple studies report worse postoperative outcomes, decreased compliance, and increased rates of mortality (7,10,12,60-63).

A study by Wikman and colleagues showed that among 1,615 patients who underwent surgery for esophageal cancer, the 2-year cumulative incidence for inpatient and outpatient psychiatric treatment was 2.5% and 4.2%, respectively (10). New cases of psychiatric disease were associated with an increased risk of mortality, with a hazard ratio of 1.65 for inpatient psychiatric care, 1.93 for outpatient care, and 2.77 for patients treated with psychotropic medication. Since the cause of death was recurrence in greater than 80% of cases, this also supports the possibility of a biochemical etiology (10).

Two meta-analyses from Pinquart and Satin also showed that depressed patients had an increased risk of mortality from 5% to 40% compared to matched subjects. In both studies, this relationship remained when subjects were controlled for clinical and medical factors (61,62).

Dimatteo and colleagues published a meta-analysis of 13 studies that found depressed patients were three times as likely to be non-compliant, and found that 63.5% of all non-compliant patients to be depressed (12). They write that reasons for non-compliance include a disbelief in the efficacy of treatment, the presence of barriers including adverse effects and financial limitations, and a lack of help and support from family members (12).

Spiegel in 2003 described three possible mechanisms for this phenomenon:
(I) Immunologic and Neuroendocrine dysfunction including disruption of the Hypothalamic-Pituitary-Adrenal Axis, and Adrenocortical Function;
(II) Depressed patients are less likely to follow-up with screening, disease treatment or general health recommendations;
(III) Many symptoms of depression are similar to those of cancer and the side-effects of chemotherapy or surgery (e.g., sleep disturbances, decreased appetite, fatigue, difficulty concentrating) (64).
Depressed patients may also be less interested in cultivating relationships with healthcare providers, have a limited capacity to understand their disease process, are less likely to seek social support, and may experience less benefit from it when they do (12,61). As described previously, depression also confers a known risk for suicide, and likely other non-cancer causes of death (8,35,65).

Interventions
To the authors’ knowledge, there are no studies that
establish criteria for treatment of cancer patients with affective disorders. This is likely due to limitations in our ability to identify these disorders, and the widespread belief that “normal” depression and anxiety behave the same as their cancer-related presentations.

Fortunately, there are several studies that are investigating possible interventions for cancer patients with depression. The use of psychotherapy is controversial in the literature. A meta-analysis by Akechi and colleagues in 2008 found that for advanced cancers, psychotherapy was effective in treating depression (66). However, another meta-analysis performed in 2017 authored by three of the same authors was less optimistic, describing that “[low] quality evidence suggests that psychotherapy is moderately more effective for the amelioration of symptoms of depression among advanced, incurable cancer patients... (67).” Heterogeneity among the studies was noted as another barrier in drawing proper conclusions.

Lydiatt and colleagues performed a randomized placebo-controlled study into the use of citalopram prophylaxis in non-depressed patients with head and neck cancer (68). When initiated before radiation, 13.8% of patients taking citalopram developed depression versus 38.7% in the placebo group (68). When started before undergoing surgery, 6.5% of patients taking escitalopram developed depression versus 11.8% in the placebo group (68).

Cognitive behavioral therapy (CBT) has also been shown to be an effective treatment for the treatment of functional gastrointestinal conditions, including irritable bowel syndrome, abdominal pain, and constipation (69,70). While these conditions share few similarities with esophageal cancer, many side effects of esophagogastric resection and bilateral vagotomy will have similar presentations. The utility of CBT and biofeedback training may benefit these patients and is worth further investigation.

Swallowing training for dysphagia has been shown to reduce the severity of depression in patients with tongue cancer (71). Though the pathophysiology of dysphagia will be different for esophageal patients, it remains one of the most common and most significant sources of emotional distress, and may warrant investigation.

Hirayama and colleagues have investigated the use of behavioral activation therapy (BAT); a form of treatment that promotes participation in daily activities instead of cognitive or pharmacologic intervention. Patients are commonly hesitant to confront death, symptom progression, and eventual loss of control. BAT seeks to alleviate depression symptoms by focusing on involvement in activities that patients enjoy, especially since participation is usually avoided (72).

As described by Hirayama... “(I) individuals suffering from depressive or anxiety conditions experience avoidance and decreased participation in normal activities; (II) this leads to decreased opportunities for them to experience joy; (III) they feel that they are overwhelmed by hardships; (IV) the value they place on their lives and themselves is diminished; (V) they pay more attention to negative information; (VI) they eventually experience more distress and depression; (VII) BAT facilitates activities they value and breaks this vicious cycle; and (VIII) this improves the depressive condition and (IX) leads to improvement in quality of life (72).”

While this study involved only ten patients, and none of the patients had esophageal cancer, the efficacy of BAT in treating depression is well-established and may be particularly suited for patients with cancer (72-74).

Summary

Depression and anxiety are common, and likely underappreciated, in esophageal cancer. The high morbidity, mortality, and rate of complications make this disease particularly high risk for emotional distress and psychiatric illness. It is possible that a fundamental overhaul of the definition of affective disorders—as they relate to cancer patients—may also be necessary.

It is also arguable that formal psychological evaluation may need to be included as a standard element of preoperative work-up and continued during the postoperative course.

This is not unprecedented. In 1991, during the early days of bariatric surgery, the national institutes of health released a consensus statement that patients must be “… selected carefully after evaluation by a multi-disciplinary team with medical, surgical, psychiatric, and nutritional expertise (75).” This was established because of the risks of bariatric procedures, and the need for long-term behavioral change following what were considered elective operations (76). Surgery for esophageal cancer has a comparable and often more severe risk profile, and causes similarly restrictive and malabsorptive changes to gastrointestinal physiology. Cancer patients, who endure arguably greater physical and emotional demands, should be worthy of similar considerations. Adding psychiatric evaluation to a standard perioperative evaluation would serve both to prospectively identify actual prevalence as well as provide treatment to
affected patients. Devoted “oncologic-psychiatry” and peer support should be offered to every patient with a new cancer diagnosis; both to improve quality of life and ensure maximal compliance to treatment.

If not just life, but quality of life, is the goal of esophageal cancer treatment, then mental well-being must be emphasized as much as surgery.

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Footnote

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