

ORIGINAL ARTICLE

A longitudinal assessment of psychological distress after oesophageal cancer surgery

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ABSTRACT

Background: Psychological distress is common among patients with oesophageal cancer. However, little is known about the course and predictors of psychological distress among patients treated with curative intent. Therefore, the aim of this study was to explore the prevalence, course and predictors of anxiety and depression in patients operated for oesophageal cancer, from prior to surgery to 12 months post-operatively.

Methods: A prospective cohort of patients with oesophageal cancer ($n = 218$) were recruited from one high-volume specialist oesophago-gastric treatment centre (St Thomas' Hospital, London, UK). Anxiety and depression were assessed prior to surgery, 6 and 12 months post-operatively. Mixed-effects modelling was performed to investigate changes over time and to estimate the association between clinical and socio-demographic predictor variables and anxiety and depression symptoms.

Results: The proportion of patients with anxiety was 33% prior to surgery, 28% at 6 months, and 37% at 12 months. Prior to surgery, 20% reported depression, 27% at 6 months, and 32% at 12-month follow-up. Anxiety symptoms remained stable over time whereas depression symptoms appeared to increase from pre-surgery to 6 months, levelling off between 6 and 12 months. Younger age, female sex, living alone and more severe self-reported dysphagia (i.e., difficulty swallowing) predicted higher anxiety symptoms. In-hospital complications, greater limitations in activity status and more severe self-reported dysphagia were predictive of higher depression.

Conclusions: Many patients report psychological distress during the first year following oesophageal cancer surgery. Whether improving the experience of swallowing difficulties may also reduce distress among these patients warrants further study.

ARTICLE HISTORY

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Introduction

Oesophageal cancer patients represent a particularly vulnerable patient group due to the poor prognosis (overall survival <15% in Europe) and the demanding curative treatment pathway including extensive surgery in combination with neoadjuvant and adjuvant oncological treatment [1]. At diagnosis, only approximately 25% of the patients are eligible for surgery and despite curatively intended treatment, the post-operative 5-year survival rate remains poor (<35%), largely due to tumour recurrence [2,3]. Previous studies have shown an increased risk of suicide following a diagnosis of oesophageal cancer, with the highest risk observed within the first 12 weeks post-diagnosis [4]. Studies also show that oesophageal cancer patients report significant psychological distress from the time of diagnosis and throughout the first year of illness [5], with anxiety and depression symptoms remaining elevated up to 4 years later [6].

Recently, large population-based cohort studies have shown that approximately 50% of surgically treated oesophageal cancer patients report emotional problems 6 months following surgery, persisting in the majority of patients at 5 years post-treatment [7], and that the occurrence of new-onset psychiatric morbidity following oesophageal cancer surgery appears to be higher than in the general population and associated with poorer post-operative survival [8]. However, there is a lack of research on the course of anxiety and depression symptoms among patients surgically treated for oesophageal cancer and predictors for poor psychological adaptation over time in this population has not yet been identified. In a previous paper, we assessed the prevalence and predictors of anxiety and depression prior to oesophageal cancer surgery [9]. This paper extends these findings with longitudinal data. The purpose of the present study was therefore to explore the prevalence, course and predictors of anxiety and depression among surgically treated oesophageal

cancer patients from prior to surgery until 12 months post-operatively.

Materials and methods

Study design and data source

Data were collected from a prospective hospital-based cohort study carried out at St Thomas' Hospital in London, UK. For the present study, patients included between 1 November 2011 and 1 March 2016, who were diagnosed with oesophageal cancer, were on a curatively intended treatment pathway, and whom consented to participate in the patient-reported outcome measures (PROM) assessment were included in the analyses. Following a diagnosis at, or referral to, St Thomas' Hospital for oesophageal resection, patients were identified by a research coordinator and invited to participate upon admission to the upper gastrointestinal inpatient ward. At this point, the study was explained fully to the patients and written informed consent was obtained. Clinical data were obtained from patients' medical charts and collected by a research coordinator, in collaboration with the surgical team, during the patient's hospital stay. The clinical data collection incorporated pre-surgical assessments of the patients, surgical information collected in theatre during the operation and post-operative information collected during the patient's post-operative hospital stay and long-term outcomes follow-up. Patients were subsequently followed up at 6 and 12 months post-surgery, by PROM assessments sent to the patient's home address to be completed and returned by post. Ethical approval was granted by the National Research Ethics Service West Midlands (REC ref 13/WM/0131).

Clinical variables

Clinical variables included in the study were tumour histology, tumour stage, neoadjuvant and adjuvant treatment status, in-hospital complications (defined as complications requiring an intervention, e.g., wound infection, pneumonia or pneumothorax) and tumour recurrence (within the 12-month follow-up period). Tumour histology was pathologically verified by the pathologist at St Thomas' Hospital and classified as adenocarcinoma or squamous cell carcinoma. Diagnostic tumour stage was classified by the Upper Gastrointestinal Multi-Disciplinary Team at Guy's and St Thomas' according to the International Union against Cancer 7th edition of the TNM system [10]. Patients completed the EORTC QLQ-OG25 questionnaire at each time-point [11]. Information on self-reported dysphagia (i.e., difficulty swallowing) at pre-surgery, 6 and 12 months post-surgery was obtained using the four-item dysphagia scale within the QLQ-OG25 and included in the analysis. Each item has four response alternatives ranging from 'not at all' to 'very much'. Responses are subsequently transformed to value on a scale ranging from 0 to 100, where higher scores correspond to more severe symptoms.

Socio-demographic variables

Socio-demographic variables included age (year of birth), sex, education level, cohabitation status, activity status (at pre-surgery, 6 months, 12 months) and work status (at diagnosis). Activity status was assessed using one question from the Patient-Generated Subjective Global Assessment Form: 'Over the past month, I would generally rate my activity as' with response alternatives ranging from 1 'No limitations' to 5 'Pretty much bedridden, rarely out of bed' [12].

Anxiety and depression

Anxiety and depression were assessed prior to oesophageal cancer surgery, then at 6- and 12-month post-surgery using the Hospital Anxiety and Depression Scale (HADS) [13]. HADS is a brief and widely used self-report measure of anxiety and depression in cancer patients, in in-hospital settings [14]. The questionnaire includes 14 items on 2 scales with 7 items corresponding to anxiety ('anxiety subscale') and 7 corresponding to depression ('depression subscale'). Items are scored from 0 to 3 yielding a total score ranging from 0 to 21 on each subscale, with higher scores reflecting more severe symptoms. According to the scoring manual [15], established cut-off scores for each subscale are: 0–7 normal status, 8–10 mild symptoms, 11–14 moderate symptoms and 15–21 severe anxiety or depression symptoms. Scores for mild symptoms (8–10) correspond to *possible* caseness of anxiety or depression disorder whereas scores of 11 and above indicate *probable* caseness of anxiety or depression disorder [13]. The recognised cut-off indicating cases of 'possible-probable' anxiety or depression disorder (scores ≥ 8 on each subscale) was used in this study to define anxiety and depression. The validity and reliability of the HADS as a short screening instrument of emotional distress in cancer patients have been shown repeatedly [16–18].

Statistical analysis

Standard descriptive statistics were calculated to present clinical and socio-demographic characteristics. Data on continuous variables are presented as means and standard deviations (SD). Categorical variables are shown as numbers (n) and percentages (%). Missing data on the HADS were handled according to the scoring manual. When one item is missing from any of the subscales, it is recommended that the score for this single item is inferred from the mean of the remaining six items. Pre-surgery, four patients had one missing item and at 6 and 12 months one patient had one missing item on the anxiety subscale, which was imputed accordingly. At pre-surgery and at 6 months one patient had one missing item on the depression subscale, which was imputed according to the scoring manual. Differences between non-responders and responders on the clinical and socio-demographic variables were analysed using Pearson's Chi-square test (or Fishers Exact test when there were small numbers in the cells).

Mixed-effects modelling with maximum likelihood estimation, including random intercepts and slopes, was used to examine potential changes over time in anxiety and

depression and to estimate the association between clinical and socio-demographic variables and anxiety and depression. Variables included in the model were time (0 = 'pre-surgery', 1 = '6-month post-surgery' and 2 = '12-month post-surgery'), age (categorised into 0 = ' ≤ 65 ' or 1 = '>65' years, as patients aged over 65 years are frequently pre-assessed by the specialist Older Persons Care Team at Guy's and St Thomas' Hospitals), sex (0 = 'male' or 1 = 'female'), university degree (0 = 'yes' or 1 = 'no'), cohabitation status (0 = 'living alone' or 1 = 'cohabitating'), in-hospital complications (0 = 'yes' or 1 = 'no') and histology (0 = 'adenocarcinoma' or 1 = 'squamous cell carcinoma'). Activity status and dysphagia scores from pre-surgery to 12 months post-operatively were included as continuous variables in the models. The statistical analyses were carried out using IBM SPSS for Windows (version 21, Chicago, IL).

Results

Patients

Throughout the study period, 260 patients underwent curatively intended surgery for oesophageal cancer and were eligible for inclusion at the pre-surgery assessment, of whom 218 (83%) were included for analysis (13 declined participation, 10 did not complete the PROM assessment, 18 were not included due to administrative reasons). At 6-month follow-up, 40 patients were not eligible (15 patients were confirmed deceased, 25 patients had yet to be included for 6-month follow-up at time of analysis). Thus, 178 were eligible for inclusion, of whom 139 (78%) completed the PROM assessment (3 patients were too unwell to complete the follow-up assessment, 36 were lost to follow-up). At 12 months, 129 patients were eligible for follow-up (27 patients were confirmed deceased, 62 patients had yet to be followed-up at time of analysis), of whom 95 (74%) completed the PROM assessment (1 patient was too unwell to participate, 32 patients were lost to follow-up). The proportion of patients with in-hospital complications were greater among responders than among non-responders at 6 months ($p < 0.05$). There were no other statistically significant differences between non-responders and responders at 6-month follow-up on clinical and socio-demographic variables. At 12 months, the proportions of male patients, patients aged below 65 years and patients diagnosed with adenocarcinoma were greater among non-responders than among those who responded to the PROM assessment ($p < 0.05$).

Information on clinical and socio-demographic variables for the sample at pre-surgery ($n = 218$) are presented in Table 1. Briefly, the majority of the patients were men (82%), aged 65 years and older (53%) and were not working at the time of diagnosis (57%). Most patients were cohabitating (79%), without a university degree (83%). The majority of the patients were diagnosed with adenocarcinoma (94%), in stage III (68%), had received neoadjuvant treatment (84%), and nearly half experienced in-hospital complications (49%).

Table 1. Clinical and socio-demographic characteristics of 218 patients surgically treated for oesophageal cancer.

	Number (%)	Mean (SD)
Age		
Years		63.94 (9.86)
<65	102 (47)	
>65	116 (53)	
Sex		
Male	178 (82)	
Female	40 (18)	
University degree ^a		
Yes	36 (17)	
No	178 (82)	
Cohabitation ^a		
Living alone	43 (20)	
Cohabiting	164 (75)	
Working at time of diagnosis ^a		
Yes	93 (43)	
No	125 (57)	
Tumour histology		
Adenocarcinoma	204 (94)	
Squamous cell carcinoma	14 (6)	
TNM stage		
I	9 (4)	
II	58 (27)	
III	144 (66)	
IV	2 (1)	
In-hospital complications ^a		
Yes	106 (49)	
No	112 (51)	
Neoadjuvant treatment		
Yes	183 (84)	
No	23 (11)	
Not known	12 (5)	
Adjuvant treatment		
Yes	115 (52)	
No	71 (33)	
Not known	32 (15)	
Tumour recurrence ^b		
Yes	49 (23)	
No	164 (75)	
Not known	5 (2)	
Activity status ^a		
Pre-surgery		1.83 (0.82)
6 months		2.18 (0.85)
12 months		2.01 (0.87)
Dysphagia ^a		
Pre-surgery		12.98 (21.26)
6 months		16.87 (20.09)
12 months		12.38 (18.23)

^aMissing data: university degree, $n = 4$; cohabitation, $n = 11$; working at diagnosis, $n = 1$; TNM stage, $n = 5$; activity status pre-surgery, $n = 2$; 6 months, $n = 2$; 12 months, $n = 1$; dysphagia pre-surgery, $n = 1$; 6 months, $n = 4$; 12 months, $n = 3$.

^bTumour recurrence within 12-month follow-up.

The standard curative treatment pathway for oesophageal cancer at St Thomas' hospital is surgery in combination with three cycles of neoadjuvant treatment and three cycles of adjuvant treatment. In cases where positive resection margins are reported post-operatively, a combination of chemoradiotherapy (CRT) is recommended for disease control. Therefore, the median time from diagnosis to surgery in this sample was approximately 5 months (147 days), during which 183 patients (84%) underwent neoadjuvant treatment. Of these, 180 patients (83%) received chemotherapy only and 3 patients (1%) had CRT in combination. Further, 115 patients (53%) completed adjuvant treatment. Of these, 65 patients (30%) received chemotherapy only, 49 patients (22%) combinational therapy (CRT) and 1 patient received radiotherapy only.

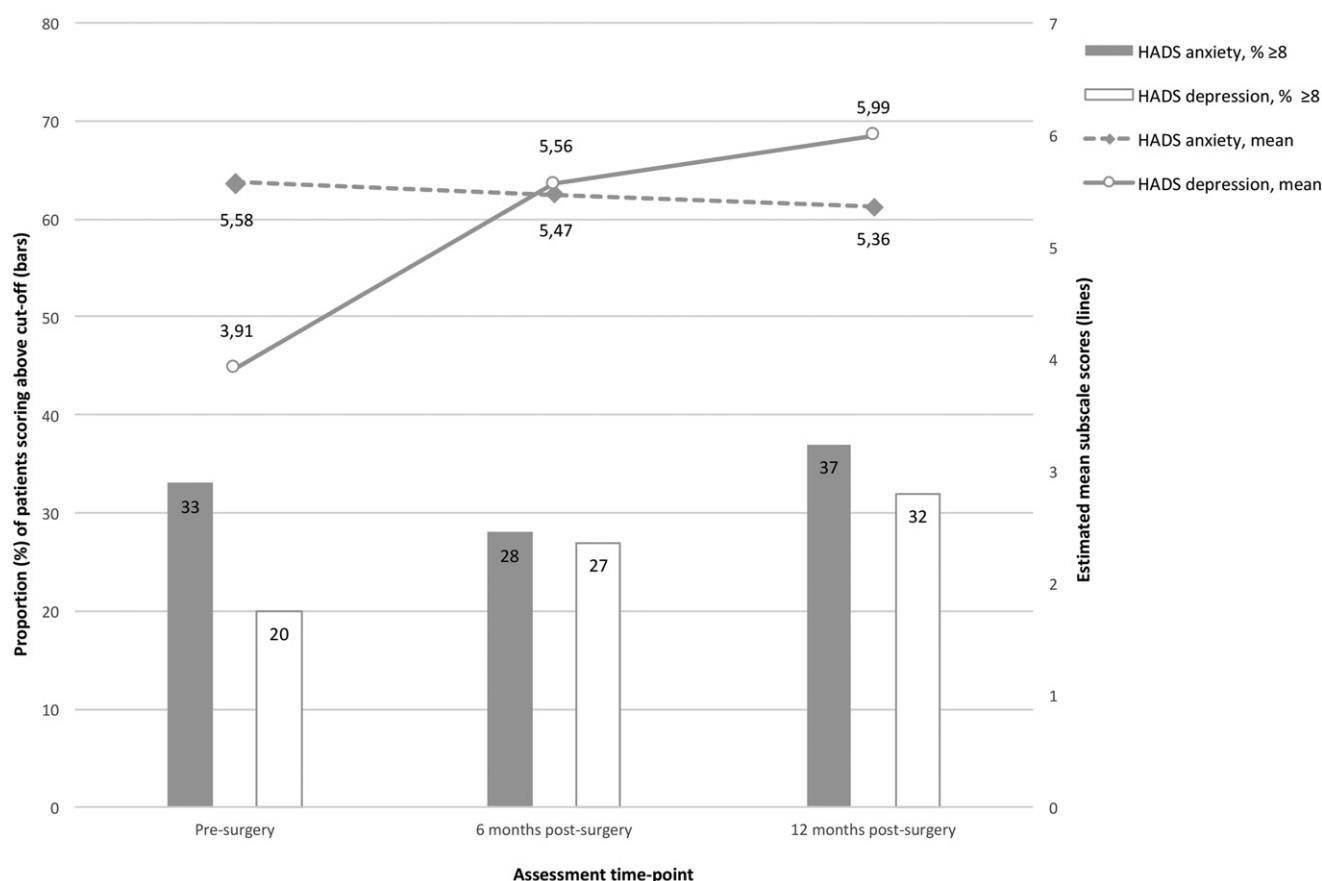


Figure 1. Proportion of patients scoring above cut-off (raw scores ≥ 8) and estimated mean scores (derived from mixed-effects models) for anxiety (unconditional linear growth model) and depression (quadratic growth curve model) measured by the Hospital Anxiety and Depression Scale (HADS) at pre-surgery, 6 months and 12 months following oesophageal cancer surgery.

Anxiety and depression at pre-surgery, 6- and 12-month post-surgery

The unadjusted mean scores on the HADS anxiety subscale prior to surgery was 5.64 (SD 4.48), at 6 months the mean score was 5.43 (SD 4.76) and at 12-month post-surgery the mean score was 5.60 (SD 4.71). The unadjusted mean scores on the HADS depression subscale were 3.91 (SD 3.67), 5.65 (SD 4.48) and 5.53 (SD 4.73) at pre-surgery, 6- and 12-month follow-up, respectively.

The proportions of patients scoring above cut-off (i.e., scores ≥ 8 on each subscale) at each time-point are shown in Figure 1. Thirty-three percent scored above the clinical threshold for possible-probable anxiety disorder prior to surgery for oesophageal cancer, at 6 months nearly one-third (28%) of patients remained anxious rising to 37% of patients at 12-month follow-up. Pre-operatively, 20% of patients reported depression above cut-off, at 6 months 27% reported depression, increasing to 32% at 12 months. Prior to surgery, 19% of patients reported anxiety only, 6% depression only, whereas 14% reported both anxiety and depression above cut-off. At 6 months, 10% reported anxiety only, 9% depression only and 18% reported anxiety and depression. At 12 months post-operatively, 10% reported anxiety only, 4% reported depression only and 28% reported co-morbid anxiety-depression symptoms.

Predictors of anxiety and depression symptoms from pre-surgery to 12-month follow-up

Estimated mean scores across time-points, on the HADS anxiety and depression subscales, derived from mixed-effect models (unconditional linear growth model for anxiety, quadratic growth curve model for depression), are shown in Figure 1.

When including clinical and socio-demographic variables in the model, anxiety symptoms did not significantly change over time ($\beta = -0.21$, 95% CI -0.65 to 0.23 , $p = 0.349$) indicating that the symptom level remained stable from pre-surgery to 12 months post-operatively. Younger age ($\beta = -1.78$, 95% CI -2.81 to -0.74 , $p = 0.001$), female sex ($\beta = 1.73$, 95% CI 0.32 to 3.14 , $p = 0.016$), living alone ($\beta = -1.33$, 95% CI -2.61 to -0.06 , $p = 0.041$), greater limitations in activity status ($\beta = 0.69$, 95% CI 0.19 to 1.19 , $p = 0.007$) and more severe self-reported dysphagia ($\beta = 0.02$, 95% CI 0.001 to 0.04 , $p = 0.033$) were significant predictors of higher anxiety symptoms. These results can also be seen in Table 2.

Depression scores significantly increased over time, with both time ($\beta = 2.26$, 95% CI 1.18 to 3.33 , $p < 0.001$) and time squared ($\beta = -0.61$, 95% CI -1.16 to 0.07 , $p = 0.027$) being statistically significant, indicating an increase in depression between pre-surgery assessment and 6-month follow-up and a levelling off of symptoms between 6- and 12-month follow-up. However, these effects disappeared (time: $\beta = 0.64$,

Table 2. Estimated outcomes of mixed-effects models for anxiety and depression from pre-surgery to 12 months post-operatively.

	Estimate (SE)	95% Confidence interval	p Value
Anxiety			
Intercept	5.68 (0.89)	3.92 to 7.45	<0.001
Time (linear)	−0.21 (0.22)	−0.65 to 0.23	0.349
Age	−1.78 (0.52)	−2.81 to −0.74	<0.001
Sex	1.73 (0.71)	0.32 to 3.14	0.016
University degree	0.99 (0.68)	−0.34 to 2.32	0.145
Cohabitation	−1.33 (0.65)	−2.61 to −0.06	0.041
In-hospital complications	−0.54 (0.52)	−1.57 to 0.49	0.303
Tumour histology	1.13 (1.06)	−0.96 to 3.24	0.287
Dysphagia	0.02 (0.01)	0.001 to 0.04	0.033
Activity status	0.69 (0.26)	0.19 to 1.19	0.007
Depression			
Intercept	2.74 (0.70)	1.36 to 4.12	<0.001
Time (linear)	0.64 (0.55)	−0.44 to 1.72	0.243
Time squared (quadratic)	0.02 (0.28)	−0.53 to 0.57	0.931
Age	−0.71 (0.41)	−1.51 to 0.10	0.085
Sex	0.44 (0.56)	−0.66 to 1.54	0.793
University degree	0.53 (0.53)	−0.51 to 1.57	0.314
Cohabitation	−0.85 (0.50)	−1.84 to 0.14	0.093
In-hospital complications	−0.94 (0.41)	−1.74 to −0.14	0.021
Tumour histology	0.47 (0.83)	−1.17 to 2.10	0.574
Dysphagia	0.03 (0.03)	0.01 to 0.04	0.001
Activity status	2.13 (0.22)	1.71 to 2.56	<0.001

SE: standard error.

95% CI −0.44 to 1.72, $p = 0.243$; time squared: $\beta = 0.02$, 95% CI −0.53 to 0.57, $p = 0.931$) when the clinical and socio-demographic variables were included in the model. In-hospital complications ($\beta = -0.94$, 95% CI −1.74 to −0.14, $p = 0.021$), greater limitations in activity status ($\beta = 2.13$, 95% CI 1.71 to 2.56, $p < 0.001$) and more severe self-reported dysphagia ($\beta = 0.03$, 95% CI 0.01 to 0.04, $p = 0.001$) were significant predictors of higher depression symptoms. This model is also presented in Table 2.

To address the possibility that changes in anxiety, depression and dysphagia post-operatively could be linked to tumour recurrence and subsequent treatment, we used independent samples *t*-test or univariate analysis of variance. This analysis showed that adjuvant treatment or recurrence (during 12-month follow-up) were unrelated to anxiety, depression and dysphagia at 6- and 12-month follow-up (data not shown).

Discussion

To date, there is limited knowledge about the course and predictors of psychological distress in the first year following oesophageal cancer surgery. To the best of our knowledge, this is the first longitudinal study to examine potential predictors of anxiety and depression symptoms, in a cohort of patients with oesophageal cancer who were treated with curatively intended surgery, from pre-surgery to 12-month post-surgery. Results show that anxiety symptoms remained stable over time whereas depression symptoms increased from pre-surgery to 6 months, levelling off somewhat between 6- and 12-month post-surgery. Younger age, female sex and living alone were identified as significant predictors of higher anxiety, whereas in-hospital complications and limited activity status predicted elevated depression symptoms. Interestingly, greater self-reported dysphagia emerged as a predictor of higher anxiety symptoms and more severe depression symptoms over time.

Although the majority of patients appeared to adjust well during the initial 12-month post-surgery, about 40% of patients scored above cut-off for a possible-probable anxiety and/or depression disorder on the HADS at 6- and 12-month follow-up. Previous studies of patients with gastrointestinal cancer have shown that patients who are initially highly anxious are also more likely to suffer persistent anxiety [19]. Results from one previous study, using the HADS to screen for psychological distress longitudinally in patients with oesophageal cancer, showed that the proportion of patients with depression scores above cut-off (i.e., scores ≥ 8) tended to increase during the first 6 months following diagnosis while scores indicating possible-probable anxiety disorder decreased over time [5]. However, the study included a small sample of both palliative and curative patients, limiting comparisons with the present results.

Consistent with the literature, younger age and female sex were associated with greater levels of anxiety [5,20,21]. Previous research highlights the potential stress-buffering effect of social support where marriage has been associated with both lower anxiety and depression in cancer patients [19,22,23]. We found that patients living alone were more likely to report higher anxiety symptoms than patients whom were cohabitating. Limitations in activity status have repeatedly been shown as a risk factor for depression in cancer patients [20,24]. In line with these findings, we found that greater limitations in activity status over time were associated with higher levels of depression. In addition, in-hospital complications such as wound infection, pneumonia or pneumothorax were also associated with higher depression scores. It may be that patients with in-hospital complications remained in hospital for a longer period of time indicating poorer condition.

Notably, self-reported dysphagia emerged as a significant predictor of both anxiety and depression symptoms over time. Progressive dysphagia and weight loss are the most

common symptoms reported by patients prior to diagnosis [25]. Therefore, re-experiencing symptoms of dysphagia post-treatment are likely to increase patient distress. Previous studies show that more than one-third of patients report deterioration over time with increased dysphagia from 6 months to 5 years post-surgery [26]. These results are interesting in light of previous studies where improved swallowing, by means of early swallowing functional training, in dysphagic tongue cancer patients has been shown to reduce severity of depression post-operatively [27]. Further, psychological interventions, including cognitive behavioural therapy (CBT), have been shown to be an effective treatment for several functional gastrointestinal conditions, with a growing body of evidence for the use of such treatments in oesophageal patients to reduce symptoms, decrease health care utilisation and improve well-being [28,29]. However, the extent to which the dysphagia reported in the present study is structural, functional or even psychosomatic was not possible to determine. Further studies to explore the relationship between development of anastomotic and pyloric strictures after surgery and anxiety and depression symptoms over time would be of interest.

Strengths of the study include the longitudinal design, the high-quality data obtained from one high-volume specialist oesophago-gastric treatment centre and high response rates at each time-point. However, anxiety and depression were assessed using a self-report screening instrument. Although the HADS has been recommended for use in oncology settings [30,31], screening tools are not diagnostic. Further, it is important to highlight that significant components of anxiety and depression are not assessed by this instrument. Consequently the HADS is likely to capture only a part of the cancer related psychological suffering that these survivors of oesophageal cancer may experience. In addition, it was not possible to assess a range of other potentially important predictor variables of psychological distress, which may affect adaptation to cancer diagnosis and treatment [32]. Previous research has shown that chemotherapy is associated with anxiety and depression [33]. However, nearly all patients in the present study received neoadjuvant treatment and this information was not included in the analyses. Work status at diagnosis and TNM stage were unrelated to anxiety or depression scores at any of the assessment points (data not shown) and thus not included in the analyses. Although anxiety and depression were assessed prior to surgery, information on a history of previous psychological morbidity was not obtained, and must be considered a major limitation of the study and results must be interpreted with caution.

In conclusion, although many patients appear to adjust well to their situation following oesophageal cancer surgery, a significant proportion of patients are affected by psychological distress during the first post-operative year. This is the first longitudinal study investigating the course and predictors of anxiety and depression symptoms among oesophageal cancer patients on a curatively intended pathway. The potential predictors identified for the development of anxiety and depression in this population may serve to inform and increase health care providers' awareness of which patients may be particularly vulnerable and burdened by distress.

Screening for emotional distress in all patients pre- and post-oesophageal cancer surgery may be warranted, and these results emphasise the importance of early identification and development of appropriate interventions for these patients to reduce psychological distress and improve quality of life in a short- and long-term perspective. Designing and evaluating interventions, possibly CBT-based treatments, targeted at reducing distress associated with self-reported symptoms of dysphagia during the first 12 months after esophageal cancer surgery warrant further study.

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Disclosure statement

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