

Title

Severe Reflux and Symptoms of Anxiety and Depression After Esophageal Cancer Surgery

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Funding

Funding was provided by the Swedish Cancer Society (grant 14 0323), the Swedish County Council (grant LS 2015-1198), and the Cancer Research Foundations of Radiumhemmet (grant 141223). The study sponsors had no role in the design of the study, data collection, analysis or interpretation of the results, the writing of the manuscript, or the decision to submit the manuscript for publication.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Data sharing

The data of this study are available on request from the first author, Dr Lagergren.

Author Contributions

Conception and design: all authors; collection and assembly of data: Dr Lagergren; data analysis: Mr Johar; interpretation of results and manuscript writing: all authors; final approval of manuscript: all authors.

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Abstract

Background: Approximately 30% of patients suffer from severe reflux after surgery for esophageal cancer, which may serve as a continuous reminder of the cancer and catalyze fear of recurrence. **Objective:** The aim of this study was to investigate the association between severe reflux and symptoms of anxiety and depression after esophageal cancer surgery. **Methods:** This was a nationwide prospective cohort study including all Swedish patients who underwent esophageal cancer surgery between 2013 and 2018. Patients reported reflux on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire module for gastroesophageal symptoms and psychological distress on the Hospital Anxiety and Depression Scale at 1 and 2 years after surgery. Repeated-measures logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for age, sex, comorbidity, body mass index, TNM classification, neoadjuvant therapy, surgery type, postoperative complications, antireflux medication, and elevated headrest at night. **Results:** Among 154 included patients, 43 (28%) and 37 (24%) reported severe reflux 1 and 2 years after surgery, respectively. No association between severe reflux and anxiety (OR, 2.1; 95% CI, 0.7–6.3) or depression (OR, 1.2; 95% CI, 0.3–4.6) was found 1 year after surgery. After 2 years, there was still no association between severe reflux and anxiety (OR, 0.9; 95% CI, 0.3–2.8) or depression (OR, 1.2; 95% CI, 0.5–3.3). **Conclusions:** Findings suggest that severe reflux is not associated with anxiety or depression after esophageal cancer surgery. **Implications for Practice:** For esophageal cancer survivors, other factors than severe reflux may be more important for the psychological recovery.

Introduction

Every year, 450,000 patients are diagnosed with oesophageal cancer worldwide.¹ Curative treatment typically encompasses surgery, chemotherapy and/or radiotherapy.² The surgical procedure involves removing a large part of the oesophagus with its tumour and usually replacing it with the stomach, which is reconstructed into a tube.³ Severe complications and burdensome symptoms following the surgery are common.⁴⁻⁹ Reflux is often considered to be an inevitable consequence of oesophageal cancer surgery, because the normal antireflux barrier is disrupted, and together with the negative intrathoracic pressure and the intraabdominal pressure, reflux is promoted across the anastomosis.¹⁰ Approximately one out of three patients report severe problems with regurgitation of stomach content (reflux).¹¹ Postoperative reflux, in turn, may induce a risk of esophagitis, aspiration pneumonia¹² and metachronous cancer in the oesophageal remnant.¹³ Postoperative symptoms after oesophagastric cancer resection have been shown to increase risk of anxiety and depression.¹⁴ Among cancer survivors, anxiety and depression are commonly seen consequences, negatively affecting quality of life, treatment compliance and survival (ref). Approximately 10-25% of cancer survivors have reported symptoms of psychological distress, irrespective of cancer trajectory time (ref). An elevated level of anxiety has been found among cancer survivors as long as up to 10 years after treatment (ref) and fear of recurrence has been associated with depression and reduced quality of life (ref). Several factors are likely to influence the development of psychological distress. To date, such potential relationships remain rather unexplored (ref). Some studies have suggested that there are associations between gastro-oesophageal reflux disease and psychopathology.¹⁵⁻¹⁷ Whether this association is applied to patients who have undergone oesophageal cancer surgery, where a gastric conduit replaces the resected oesophagus, is not yet clarified. Also, the correlation between objective severity of gastro-oesophageal reflux and symptom severity perceived by the patient

seems to be poor.¹⁸⁻¹⁹ indicating an interplay of psychological factors. Recovery does not only depend upon surgical success, but also on how the patients view their illness and their ability to cope with the new situation.²⁰ Physical and psychosocial suffering experienced by patients with cancer can evoke feelings of symptom distress (ref). This distress can be defined as an individual's perception and response to symptoms (ref). Physical symptoms of a cancer disease with its treatments can predispose patients to distress (ref). Severe postoperative reflux may serve as a continuous reminder of the cancer and catalyse fear of recurrence.²¹ These patients may possibly be more frequently confronted by the risk of recurrence and prone to develop anxiety and depression. Understanding the impact of oesophageal cancer surgery and its long-term effects is essential for survivorship programmes to develop adequate management strategies with the aim of improving patients' quality of life. Therefore, this study aims to describe the prevalence of anxiety and depression in patients who suffered from reflux after oesophagectomy for cancer and to investigate the association between severe reflux and symptoms of anxiety and depression.

Methods

Study design

This was a nationwide, population-based cohort study using data from the XXX study, which was initiated in 2013 and designed to improve outcomes for oesophageal cancer surgery survivors. All Swedish patients who underwent oesophagectomy for cancer between January 1, 2013 and April 30, 2018, were eligible for inclusion. Patients with previous psychiatric history and cognitive impairment were excluded. Participants who gave informed consent were included in the study one year after surgery and were followed up the following year. The study was approved by the regional ethical review board in XXX, Sweden (diary number 2013/844-31/1). A patient research partnership group consisting of former oesophageal cancer patients was involved in the planning of study.

Data collection

The organisation of the nationwide data collection has been described in detail elsewhere.¹¹ In brief, eligible patients were identified through collaboration with all eight pathology departments in Sweden in hospitals where these operations were conducted. At inclusion, one year after surgery, a research nurse visited the patients in their home to guide them through self-reported computer-based questionnaires to collect patient-reported outcomes and anthropometric measurements, including height and weight. Two years after surgery, the same questionnaires were sent to the patients and returned by post. Clinical data were collected from medical records and included tumour histology, TNM classification, cancer treatment, and postoperative complications. To ensure consistency and uniformity of the data collection, two researchers reviewed each medical record according to a predefined study protocol. An independent researcher performed cross-validation of randomly selected protocols. Data on patient characteristics were collected by linking the personal identity number assigned to each Swedish resident to national health data registries. Socio-demographic information was obtained via linkage to the Longitudinal Integration Database for Health Insurance and Labour Market, which holds registration since 1990 and is updated yearly.²² Information on comorbidities were obtained from the Swedish Patient Registry and the Swedish Cancer Registry. The Swedish Register of the Total Population was used to retrieve survival data. All these registries hold nearly 100% complete nationwide information.^{23,24}

Exposure

The study exposure was severe reflux measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) module for gastro-oesophageal symptoms (OG25),²⁵ which comprises six symptom scales (dysphagia, eating

restrictions, reflux, odynophagia, pain and discomfort, and anxiety) and ten single items (eating in front of others, dry mouth, trouble with taste, body image, trouble swallowing saliva, choking when swallowing, trouble with coughing, trouble talking, weight loss, and hair loss). There are four response alternatives: “not at all”, “a little”, “quite a bit”, and “very much”. The health-related quality of life (HRQL) scores were transformed into a scale ranging from 0 to 100 where higher scores represent more problems. Severe reflux was identified in the questions “Have you had acid indigestion or heartburn?” and “Has acid or bile coming into your mouth been a problem?” Patients who answered “quite a bit” or “very much” to either of the questions were considered to have severe reflux.

Outcomes

The main outcomes were symptoms of anxiety and depression (combined and separately) assessed with the Hospital Anxiety and Depression Scale (HADS)²⁶ at one and two years postoperatively. HADS is a widely used self-reported measure of anxiety and depression in cancer patients.²⁷ The questionnaire contains separate subscales for anxiety and depression. Each subscale has seven questions and each question is graded on a 4-point Likert scale ranging from 0 to 3, with a maximum subscale score of 21. A higher score represents more symptoms. Subscale scores ≥ 8 are defined as possible/probable cases of anxiety and depression, respectively.²⁸ The questionnaire is validated in a Swedish sample.²⁹

Potential confounders

Potential confounders were age, sex, comorbidity, body mass index (BMI), smoking habits, alcohol intake, tumour histology and TNM classification, neoadjuvant therapy, type of surgery, postoperative complications, and reflux symptom management. Comorbidities were classified according to the Charlson Comorbidity Index.^{30,31} BMI was calculated based on the objective measurements of height and weight performed by the research nurse at the home

visit. Smoking habits and alcohol intake were self-reported through the questionnaires. Tumour histology and TNM classification, neoadjuvant therapy and type of surgery were retrieved from the medical records. Postoperative complications were classified according to Clavien Dindo.^{32,33} Reflux symptom management was assessed by two study specific questions in the computer-based questionnaires: “Do you use medication for reflux problems?” and “Do you sleep with elevated headrest?”.

Statistical analyses

With 5%, and at least 20% prevalence of anxiety and depression in the unexposed and exposed groups, respectively, sampling ratio of 0.4 (exposed/unexposed), 5% level of significance, one sided test comparing two sample proportions, the study has more than 80% power. Descriptive statistics were presented as counts (n), proportions (%) and mean scores (MS) with 95% confidence intervals (95% CI). Summary statistics were used to present patient characteristics with Fisher’s exact test and Student’s t-test was used to compare patients with and without reflux at one and two years. Moreover, prevalence of anxiety and depression between patients with and without severe reflux was compared using Fisher’s exact test and 5% level of significance was used in statistical tests.

Associations between severe reflux and anxiety/depression (one and two years postoperatively) were analysed with repeated measure logistic regression model to accommodate correlated measurements from the same patient (with Generalized estimating equations [GEEs] using Proc Genmod with a time interaction term and an unstructured working correlation matrix assumption). Exposure effects were presented as odds ratios (ORs) with 95% CI. Three models were used to assess the influence of covariates: Model 1 was the crude analysis; Model 2 included adjustments for age (continuous), sex, Charlson Comorbidity Index score (0, 1, or ≥ 2), BMI (<30 or ≥ 30), smoking habits (ever or never), alcohol intake (ever or never), tumour histology (adenocarcinoma or squamous cell

carcinoma), TNM classification (0-I, II, or III-IV), neoadjuvant therapy (yes or no), type of surgery (open, minimally invasive, or hybrid), and Clavien Dindo score (0-II or III-IV).

Model 3 was further adjusted for reflux symptom management (medication or elevated headrest, yes or no). All data management and statistical analyses were conducted by a senior statistician (AJ) with expertise in HRQL analyses using SAS version 9.4 (Cary, NC).

Results

Patients

Between January 1, 2013 and April 30, 2018, 675 patients underwent oesophageal cancer surgery in Sweden. Of these, 511 (75%) survived for at least one year, 85 were not reachable, 7 were excluded because of previous psychiatric history and 2 of cognitive impairment, leaving 417 patients eligible for inclusion. Of those eligible, 284 patients (68%) consented to participate in the study and complete data for the two assessments were available for 154 individuals (37%). The patients' mean age was 66 (standard deviation 9) years (Table 1) and the majority were men (86%), without any comorbidities (50%). The most common histological type of cancer was adenocarcinoma (84%) treated with neoadjuvant therapy (81%) and open surgery (40%). One hundred and forty-seven patients were prescribed proton pump inhibitors, out of which 93 stated that they used antireflux medication.

Severe reflux after oesophagectomy

One year after surgery, 43 patients (28%) were categorised as having severe reflux (Table 1). These individuals reported higher scores of reflux (MS 63, 95%CI: 58-67) compared to patients without reflux (MS 12, 95%CI: 9-15). Two years after surgery, the proportion of patients with severe reflux was lower (n=37, 24%), but the reflux symptoms were somewhat more burdensome (MS 67, 95%CI: 62-72). The groups were comparable regarding patient and clinical characteristics except that more patients with severe reflux used antireflux

medication. Also, at 2 years, fewer patients with severe reflux had received neoadjuvant therapy.

Severe reflux and symptoms of anxiety and depression

The prevalence of anxiety and depression was similar between patients with and without severe reflux showing no statistically significant differences (Table 2). No increased risk of anxiety (OR 2.1, 95%CI: 0.7-6.3), depression (OR 1.2, 95%CI: 0.3-4.6) or anxiety/depression (OR 1.4, 95%CI: 0.5-4.0) was found in patients with severe reflux at one year after surgery. There was still no association between severe reflux and anxiety (OR 0.9, 95%CI: 0.3-2.8), depression (OR 1.2, 95%CI: 0.5-3.3) and anxiety/depression (OR 0.9, 95%CI: 0.4-2.6) two years after surgery (Table 3)

Discussion

In this nationwide, population-based study, severe reflux after oesophageal cancer surgery did not increase the risk of anxiety or depression one or two years after surgery.

Our hypothesis for this study, that persistent reflux symptoms might be a reminder of the severe cancer diagnosis, the extensive surgery and the following life changes, and thereby accompanied by symptoms of anxiety and depression could not be verified. This result suggests that factors other than reflux are involved in patients' psychological recovery. From a patient perspective, the changed life situation after diagnosis and treatment of cancer, including the cumulative effect of symptoms¹⁴ is essential for the psychological well-being. However, the presence of comorbidities, a more advanced tumour stage, a previous psychological history or a patient's family situation may be as important as symptom presentation on the impact on quality of life⁴²⁻⁴⁴ and warrant further investigation. Untreated mental health disorders negatively influence the underlying cellular and molecular processes that facilitate the progression of cancer⁴⁵ and depression is associated with poor compliance to

medical therapies⁴⁶ and therefore, it is important to identify factors that might catalyse these problems.

The magnitude of the problem with postoperative reflux was recently shown in a European multicentre study where among 876 patients, 70% reported heartburn within 6 months of oesophageal cancer surgery. More than 50% of patients reported that they had sought medical treatment for postoperative symptoms and that proton pump inhibitors were the most commonly used postoperative medication.³⁵ In a review, it was concluded that functional disorders, of which postoperative reflux was one, did not significantly impact patients' quality of life.³⁶ However, in a relatively recent study including 158 patients who had undergone oesophagectomy for cancer, postoperative reflux was associated with reduced global quality of life and more symptoms of fatigue, nausea and vomiting, dyspnoea and insomnia.³⁷ These conflicting results show the need to better understand how the consequences of surgery influence the survivors' well-being.

Compared to the general population, the prevalence of anxiety and depression is often higher among individuals with cancer, but estimates may vary depending on type and stage of the tumour, treatment setting and screening methods.³⁸ In a study, based on data from a Swedish sample of 6659 individuals, randomised from the total population aged 65-80 years old, the prevalence of anxiety and depression was 11% and 10%, respectively.³⁹ In a large population-based study including approximately 6,200 individuals from the United Kingdom between 25 and 65 of age, the prevalence of anxiety was 13% for mild anxiety and 7.5% for moderate to severe anxiety, while 9.6% had mild depression and 6.9% moderate to severe depression.⁴⁰ Oesophageal cancer surgery has previously been shown to entail increased levels of anxiety and depression.⁴¹ In the current study, anxiety in particular, seemed to be elevated for patients with reflux. However, future studies including a larger study sample are needed to confirm the results.

Even though no associations between severe reflux and symptoms of anxiety and depression were found, the results contribute with pieces of a puzzle that eventually will lead us towards evidence-based care for oesophageal cancer survivors. As with many cancer-related morbidities, we do not have a full understanding of the consequences following cancer treatment. This study is to inform and improve care for patients experiencing severe reflux after oesophagectomy for cancer. With or without postoperative reflux symptoms, it is important that oncology counselling, beyond the end of treatment, is made available for cancer survivors, linking with cancer teams and clinical nurse practitioners to enable referral of individuals in need of support and treatment.

The prospective and population-based design with relatively high participation rate and use of well-validated questionnaires strengthens the study and counteracts recall, selection and information bias. Lack of data on psychological status at baseline prevents adjustments for potential preoperative differences between the groups. However, such differences should not be dependent on reflux. Another limitation is the absence of data on psychiatric medication, since treatment with anxiolytics and antidepressants has been shown to cause reflux.³⁴ Yet, patients with a previous psychiatric history and cognitive impairment were excluded, so this bias should be limited. However, individuals with previous psychological history may be particularly vulnerable and the exclusion of this group might therefore have contributed to an underestimation of the anxiety and depression prevalence. Even though the participation rate was 68%, we cannot rule out that non-participation influenced the results, since responders tend to be physically and psychologically healthier. The observational design cannot rule out unmeasured confounding. Adjustments for several covariates in the analyses reduced the risk, but residual confounding cannot be completely eliminated.

In conclusion, this nationwide longitudinal study suggests that severe reflux after oesophageal cancer surgery is not associated with anxiety or depression, but larger studies are needed to establish this lack of association.

Acknowledgements

We would like to thank all participants of the study for sharing their experiences with us and the members of the patient research partnership group for their invaluable contribution and comments throughout the development of the publication.

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Table 1. Demographic and clinical characteristics one and two years after oesophagectomy for patients with and without severe reflux

	All patients Number (%)	One year		Two years	
		Severe reflux Number (%)	Without severe reflux Number (%)	Severe reflux Number (%)	Without severe reflux Number (%)
	154 (100)	43 (28)	111 (72)	37 (24)	117 (76)
Age					
Mean±SD	68±8	66±8	68±8	67±10	69±7
Sex					
Men	132 (86)	37 (86)	95 (86)	31 (84)	101 (86)
Women	22 (14)	6 (14)	16 (14)	6 (16)	16 (14)
Charlson comorbidity index score					
0	77 (50)	18 (42)	59 (53)	16 (43)	61 (52)
1	49 (32)	16 (37)	33 (30)	11 (30)	38 (32)
≥2	28 (18)	9 (21)	19 (17)	10 (27)	18 (15)
Body mass index					
<30	144 (94)	40 (93)	104 (94)	35 (97)	106 (94)
≥30	10 (6)	3 (7)	7 (6)	1 (3)	7 (6)
Smoking habits					
Ever	128 (83)	37 (86)	91 (82)	31 (84)	97 (83)
Never	26 (17)	6 (14)	20 (18)	6 (16)	20 (17)
Alcohol intake					
Ever	125 (82)	37 (86)	88 (80)	31 (84)	94 (81)
Never	28 (18)	6 (14)	22 (20)	6 (16)	22 (19)
Tumour histology					
Adenocarcinoma	129 (84)	37 (86)	92 (83)	32 (86)	97 (83)
Squamous cell carcinoma	25 (16)	6 (14)	19 (17)	5 (14)	20 (17)
TNM classification					
0-I	63 (41)	20 (47)	43 (39)	17 (46)	46 (39)
II	47 (31)	14 (33)	33 (30)	10 (27)	37 (32)
III-IV	44 (29)	9 (21)	35 (32)	10 (27)	34 (29)
Neoadjuvant therapy					
Yes	124 (81)	34 (79)	90 (81)	25 (68)*	99 (85)
No	30 (19)	9 (21)	21 (19)	12 (32)	18 (15)
Type of surgery					
Open	61 (40)	18 (42)	43 (39)	12 (32)	49 (42)
Minimally invasive	42 (27)	9 (21)	33 (30)	9 (24)	33 (28)
Hybrid	51 (33)	16 (37)	35 (32)	16 (43)	35 (30)
Clavien Dindo score (postoperative complications)					
0-II	102 (66)	31 (72)	71 (64)	23 (62)	79 (68)
III-IV	52 (34)	12 (28)	40 (36)	14 (38)	39 (32)
Antireflux medication					
Yes	93 (60)	38 (88)*	55 (50)	30 (81)*	63 (54)
No	61 (40)	5 (12)	56 (50)	7 (19)	54 (46)
Elevated headrest					
Yes	32 (21)	11 (26)	21 (19)	6 (16)	26 (22)
No	122 (79)	32 (74)	90 (81)	31 (84)	91 (78)

SD=Standard deviation, * Indicates statistically significant differences ($p<0.05$) between patients with and without severe reflux

Table 2. Prevalence of symptoms of anxiety and depression in oesophagectomy patients with and without severe reflux

		One year		Two years	
		Severe reflux	Without severe reflux	Severe reflux	Without severe reflux
		Number (%)	Number (%)	Number (%)	Number (%)
		43 (28)	111 (72)	37 (24)	117 (76)
HADS-Anxiety score	<8	36 (84)	103 (93)	30 (81)	100 (85)
	≥8	7 (16)	8 (7)	7 (19)	17 (15)
HADS-Depression score	<8	38 (88)	102 (92)	28 (76)	96 (82)
	≥8	5 (12)	9 (8)	9 (24)	21 (18)
HADS-Anxiety/Depression ¹		9 (21)	13 (12)	10 (27)	26 (22)

HADS=Hospital Anxiety and Depression Scale. A score of 8 or above indicates possible/probable cases of anxiety and/or depression. ¹If either HADS-anxiety or HADS depression ≥8, or if both HADS-Anxiety and HADS depression ≥8

Table 3. Risk of anxiety and depression in oesophagectomy patients with severe reflux compared to oesophagectomy patients without severe reflux, presented as odds ratios (OR) with 95% confidence intervals (CI)

	One year (n=43)			Two years (n=37)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anxiety	1.8 (0.6-5.1)	1.7 (0.6-4.9)	2.1 (0.7-6.3)	0.8 (0.3-2.5)	0.8 (0.3-2.3)	0.9 (0.3-2.8)
Depression	1.0 (0.3-3.8)	1.0 (0.3-3.6)	1.2 (0.3-4.6)	1.0 (0.4-2.7)	1.1 (0.4-2.8)	1.2 (0.5-3.3)
Anxiety/Depression	1.4 (0.5-3.7)	1.3 (0.5-3.5)	1.4 (0.5-4.0)	0.9 (0.4-2.3)	0.9 (0.4-2.2)	0.9 (0.4-2.6)

Model 1 - crude; Model 2 – adjusted for age, sex, Charlson Comorbidity Index score, body mass index, smoking habits, alcohol intake, tumour histology, TNM classification, neoadjuvant therapy, type of surgery, and Clavien Dindo score; Model 3 – as model 2 and further adjusted for antireflux medication and elevated headrest.