Presence of symptom clusters in surgically treated patients with esophageal cancer

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Title: Presence of symptom clusters in surgically treated patients with esophageal cancer – implications for survival

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Condensed abstract: Symptoms experienced by surgically treated esophageal cancer patients cluster together and these clusters appear to have prognostic value. Results highlight the need to consider the effects of symptom clusters on patient outcomes such as post-operative survival.

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Abstract

Background: It is not known whether symptoms cluster together after esophageal cancer surgery or whether such symptom clusters are associated with survival in these patients.

Methods: Data from a prospective Swedish nationwide cohort study of surgically treated esophageal cancer patients recruited between 2001 and 2005 were used. General and esophageal cancer specific symptoms were assessed using the EORTC QLQ-C30 and the QLQ-OES18 6 months post surgery. Associations between symptom clusters and survival were analyzed using Cox proportional hazards models, providing hazard ratios (HR) with 95% confidence intervals (CI), adjusted for other known prognostic factors.

Results: Among 402 patients reporting symptoms 6 months following surgery, three symptom clusters were identified. The first symptom cluster ('*fatigue/pain*') was characterized by symptoms of pain, fatigue, insomnia and dyspnea and was present in 30% of patients. The second symptom cluster ('*reflux/cough*') was characterized by symptoms of dry mouth, problems with taste, coughing and reflux and was present in 27% of patients. The third symptom cluster ('*eating difficulties*') was characterized by appetite loss, dysphagia, eating difficulties and nausea/vomiting and was present in 28% of patients. Presence of the reflux/cough and eating difficulties symptom clusters were associated with a statistically significantly increased risk of mortality (adjusted HR 1.43, 95% CI 1.08 – 1.89 and, adjusted HR 1.41, 95% CI 1.06 – 1.87, respectively).

Conclusion: Symptoms experienced by surgically treated esophageal cancer patients appear to cluster together, and the presence of these symptom clusters have strong prognostic value.

Keywords: symptoms; clusters; health-related quality of life; prospective; mortality.

Introduction

Esophageal cancer is an aggressive disease associated with an extremely poor prognosis. The overall 5-year survival rate is as low as 10% in Europe.[1] Surgical resection is the most established potentially curative treatment.[2] The prognosis is unfavorable even when the tumor is surgically removed, with a post-operative 5-year survival rate of 31%.[3] The operation is more extensive than most other standard surgical procedures and is associated with a substantial negative impact on patients' health-related quality of life (HRQOL), [4-6] with patients suffering persistent problems with physical function and specific symptoms even at 3 years postoperatively.[7, 8] Although the majority of patients have recovered in terms of HRQOL functions and symptoms, and report scores similar to those of the background population at 5 years, a substantial minority of long-term survivors appear to further deteriorate over time.[9]

Cancer patients often experience multiple concurrent symptoms as a result of their disease and treatment, and these tend to cluster together in systematic ways. For example, symptoms of fatigue, insomnia and depression are often experienced simultaneously.[10, 11] In the past decade, the interest in the impact of symptom clusters on patient outcomes has increased, and symptom clusters may have a negative impact on survival in advanced cancer.[12, 13] Esophageal cancer patients experience numerous symptoms following surgical treatment and previous studies have evaluated the impact of individual HRQOL functions and symptoms on patient outcomes. Several aspects have been identified as prognostic indicators for survival in this group of cancer patients. Better pre-treatment physical and role functioning as well as global quality of life (QOL) are associated with better survival.[14] Other studies have demonstrated an association between poor pre-treatment appetite loss, [15-17] fatigue, [18-20] dyspnea, [20, 21] reflux[18] and an increased mortality risk. Moreover, poor post-operative global QOL, physical function and social function, as well as

symptoms of fatigue, pain, dyspnea, appetite loss, dysphagia and esophageal pain have been shown to predict mortality independently of established prognostic factors.[22]

Although studies indicate a prognostic role of individual HRQOL functions and symptoms, it is not known whether post-surgery symptoms cluster together in a particular manner, or what the implications are of the presence of any such symptom clusters on patient outcomes. Therefore, we aimed to establish whether the symptoms experienced by esophageal cancer patients 6 months following surgery cluster together, and whether the presence of such symptom clusters are predictive of survival.

Methods

Study design

A Swedish nationwide, prospective cohort study of esophageal cancer patients was conducted between April 2, 2001 and December 31, 2005. All patients in Sweden diagnosed with esophageal or esophago-gastric junctional cancer, whom underwent curatively intended surgery during the study period, were eligible for inclusion. The cohort included 90% of all surgically treated patients in Sweden during this time-period. Patients were followed-up with measures of HRQOL 6 months post-surgery. Ethical approval was granted by the Regional Ethical Review Board in Stockholm, Sweden, and informed consent was obtained from all patients.

Clinical data collection

The prospective data collection has been described in full elsewhere.[23, 24] In brief, data were collected via a nationwide network of hospital departments and physicians involved in the diagnostics and treatment of patients with esophageal or esophago-gastric junctional cancer in

Sweden, and registered in the Swedish Esophageal and Cardia Cancer (SECC) database. Based on a pre-defined study protocol, data on patient and tumor characteristics as well as information regarding hospital, surgical treatment and complications were collected prospectively through manual review of medical records. Information on mortality was obtained via linkage to the 100% complete Swedish Register of the Total Population.

Measures

Several socio-demographic and clinical characteristics were assessed in the study and categorized as follows; age (<60, 60-74, or ≥75 years), sex (male or female), tumor stage (0-I, II, or III-IV), tumor histology (squamous cell carcinoma or adenocarcinoma), operation type (esophageal resection, cardia resection, extended total gastrectomy, or total gastrectomy and esophageal resection), post-operative complications (0, 1, or >1) and co-morbidities (0 or ≥1). Information on these characteristics was gathered from medical records. Post-operative complications were pre-defined and included perioperative bleeding, leakage or perforation of the anastomosis, stricture of the anastomosis, wound infection needing treatment, wound rupture, gastric perforation, intra-abdominal or intrathoracic abscess, ileus, thoracic duct injury, re-intubation or need for prolonged mechanical ventilation, paresis of the recurrent laryngeal nerve, pneumonia, pulmonary thrombosis, and myocardial infarction. Co-morbidity included angina, heart failure, hypertension, diabetes, pulmonary disease, renal failure, liver failure and other cancer.

To assess symptoms, two HRQOL questionnaires were used in the study. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30[25] was used to assess symptoms common among cancer patients in general, while the esophageal-specific module QLQ-OES18[26] was used to measure symptoms common among esophageal cancer patients in particular. The QLQ-C30 incorporates five functional scales, one global

QOL scale, one item about financial difficulties, three symptom scales assessing pain, fatigue and nausea/vomiting, and five single items addressing symptoms of dyspnea, sleeping difficulties, appetite loss, constipation and, diarrhea. The EORTC QLQ-OES18 contains four symptom scales addressing symptoms of dysphagia, eating difficulties, reflux and esophageal pain, and six single items assessing trouble swallowing saliva, choking when swallowing, dry mouth, trouble with taste, coughing or talking. The three symptom scales and five single symptom items from the QLQ-C30 and all symptom scales and single items from the QLQ-OES18 were included in the analyses. Responses to the functional scales, global QOL and the financial difficulties question were not included in the present analyses as the aim of the study was to cluster symptoms not functions. Items were scored on a four-point scale; (1) "not at all", (2) "a little", (3) "quite a bit", and (4) "very much", referring to symptoms experienced during the past week. For the purposes of the current analyses, symptoms were recoded as binary variables to represent "presence" (for a response of 3 or 4) or "absence" (for a response of 1 or 2) of symptoms. This cut-off was based on previous work and clinical experience, representing a level of symptoms which would likely be noticed by clinicians in practice.[6, 27]

Statistical analyses

The symptom clustering was performed in two steps. In the first step, symptoms were clustered using the principal component analysis (PCA) method. In order to address the sensitivity of the final clusters to selected clustering methods, hierarchical cluster analysis (HCA) method was also used to compare the final clusters in this first step.[28, 29] These methods (PCA and HCA) group symptoms in clusters so that the symptoms are highly correlated within their own cluster and have very low correlations with symptoms in other clusters. The splitting criterion with maximum eigenvalue of 1 was used to select the final cluster solution from the PCA method. Moreover, for the HCA method, the lowest maximum $1 - R^2$ ratio value for a variable was used as the measure of clustering fit and to select the

final cluster solution. Among 18 symptom scales and single items, 14 symptoms with at least 15% prevalence in the sample were selected for clustering (including symptoms of pain, fatigue, nausea/vomiting, dyspnea, sleeping difficulties, appetite loss, diarrhea, dysphagia, eating difficulties, reflux, esophageal pain, dry mouth, trouble with taste, cough).[30] In the second step, patients were assigned cluster membership if they suffered from at least 50% of symptoms from within a symptom cluster (i.e. symptom cluster present).[13] Hence a patient could belong to more than one cluster.

Chi-square test was used to examine between cluster differences on baseline socio-demographic and clinical characteristics. Multivariable logistic regression analysis, providing adjusted odds ratios (OR) with 95% confidence intervals (CI), was used to assess the baseline socio-demographic and clinical characteristics of final clusters. The symptom clusters were analyzed in relation to survival by the Kaplan-Meier method. Statistical significance was tested at the 5% level by the log-rank test. A Cox proportional hazard model, providing adjusted hazard ratios (HR) with 95% confidence intervals (CI), was used to analyze the 5-year survival of final clusters, controlling for confounding by baseline socio-demographic and clinical characteristics (using the categorizations of variables as described in the measures section above). Logistic regression model was used to assess the discriminative power of these clusters using the area under the ROC curve. Due to the potential overlapping cluster membership, interactions between clusters were also tested at the 5% level of significance using Wald Chi-square test. PROC VARCLUS (SAS 9.2, SAS Institute, Cary, NC, USA) was used for PCA and HCA (with centroid option) clustering methods and SAS 9.2 was used for other data analyses.

Results

Patient characteristics

During the study period, 616 patients were included in the cohort. Of these, 110 (18%) patients died within 6 months of surgery. Therefore, 506 patients were eligible for the present study and of these, 402 (79%) patients responded to the 6-month follow-up symptom assessment. There were no statistically significant differences between responders and non-responders on any of the baseline clinical or socio-demographic characteristics. Baseline characteristics of the participating patients are detailed in Table 1. Based on the total group (n=402), patients were predominantly male (81%) and aged between 60 and 74 years (58%). The majority of patients were diagnosed with adenocarcinoma of the esophagus (76%) of tumor stage III (41%), and had undergone esophageal resection (76%). At least one complication was recorded in 133 (33%) patients, and the majority of patients (59%) had one or more co-morbidity.

Cluster solution and characteristics of symptom clusters

The final cluster solutions from PCA and HCA were identical with the exception of the symptom diarrhea which formed a single symptom cluster when using the HCA method. All other symptoms clustered into identical clusters produced by both methods. We therefore selected the three-cluster solution by using the PCA method.

Baseline characteristics of the three symptom clusters are presented in Table 1. The first cluster was characterized by symptoms of pain (general and esophageal), fatigue, insomnia and dyspnea. This cluster was named the '*fatigue/pain*' (FP) symptom cluster. Among the 402 patients who responded to the symptom assessment at 6 months post-surgery, this cluster was present (i.e. meeting criteria for cluster membership by reporting at least 50% of symptoms in the cluster) in 122 (30%) patients and absent in 280 (70%). The most

prevalent symptom in this cluster was fatigue (97%). Cluster 2 was characterized by symptoms of dry mouth, problems with taste, coughing and reflux. This cluster was named the '*reflux/cough'* (RC) symptom cluster. This symptom cluster was present in 107 (27%) patients and absent in 295 (73%). The prevalence of each of the four symptoms within this cluster was approximately 60%. The third cluster was defined predominantly by symptoms related to eating, such as appetite loss, dysphagia, eating difficulties and nausea/vomiting, and was named the *'eating difficulties'* (ED) symptom cluster. The ED cluster was present in 112 (28%) patients and absent in 290 (72%). The most prevalent symptoms in this cluster were eating difficulties (95%) and appetite loss (84%). The composition of the symptom clusters is presented in Table 2.

Univariable differences on baseline characteristics within the clusters were assessed with Chi-square analyses. Younger age, higher tumor stage, squamous-cell carcinoma and more complications were associated with presence of the FP symptom cluster (all at $p<0.05$). Squamous-cell carcinoma and more complications were associated with presence of the RC symptom cluster, whereas with a higher tumor stage and more complications were associated with presence of the ED symptom cluster (all at $p<0.05$). No other statistically significant univariable differences were observed within clusters. Subsequent multinomial logistic regression analysis, adjusting for all other baseline characteristics, showed that compared with squamous-cell carcinoma, patients with adenocarcinoma were less likely to be assigned cluster membership to the FP symptom cluster (adjusted OR 0.49, 95% CI 0.28 – 0.84) and the RC symptom cluster (adjusted OR 0.54, 95% CI 0.32 – 0.94). Compared with having >1 complication, patients with no complications were less likely to be assigned cluster membership to the FP symptom cluster (adjusted OR 0.42, 95% CI 0.21 – 0.84) and the ED symptom cluster (adjusted OR 0.46, 95% CI 0.23 – 0.93).

Presence of symptom clusters and mortality

Median survival times for the FP, RC and ED symptom clusters were 18.13, 21.16 and 21.17 months, respectively. Of the 402 patients responding to the 6-month follow-up symptom assessment, 124 (31%) were alive at 5 years. Figure 1 shows the Kaplan-Meier estimates of survival, illustrating the significantly reduced 5-year survival estimates (shown in months) for the presence of symptom clusters (log-rank test, $p<0.001$). Cox proportional hazards modeling demonstrated that symptom cluster was a significant predictor of mortality (Table 3). Following adjustment for age, sex, tumor stage, tumor histology, operation type, post-operative complications and co-morbidities, presence of the RC and ED symptom clusters were associated with a statistically significantly increased risk of mortality (HR 1.43, 95% CI 1.08 – 1.89 and, HR 1.41, 95% CI 1.06 – 1.87, respectively). Moreover, area under the ROC curve was 0.79 which shows that the clusters discriminate well between 5-year survivors and non-survivors. As patients could be assigned membership to more than one cluster (31 patients belonged to all three clusters, 65 to both the PF and ED clusters, 48 to both the RC and ED clusters, and 55 to both the FP and RC clusters), interactions between the symptom clusters were also tested by introducing product terms in the Cox model (by using Wald Chi-square test at the 5% level of significance). No interactions emerged as statistically significant.

Discussion

Using PCA, three symptom clusters were identified based on 14 self-reported general and esophageal cancer specific symptoms six months following curatively intended surgery. The identified symptom clusters were named ‘fatigue/pain’, reflux/cough’ and ‘eating difficulties’ based on the composition of symptoms forming each cluster. The presence of symptom

clusters at six months following surgery were significant predictors of survival duration, with the RC and ED symptom clusters emerging as statistically significant predictors of 5-year mortality. Presence of these symptom clusters conferred an approximately 40% increased risk of mortality. Importantly, the multivariable adjusted survival analysis demonstrated that these associations existed over and above what could be explained by other known prognostic factors, suggesting an important independent prognostic role of self-reported symptom clusters six months following esophageal cancer surgery.

Strengths of the study include the population-based design, the high participation rate and large sample size, the high quality of clinical data, the use of well-validated questionnaires, and adjustment for other known prognostic factors. This is the first study to examine symptom clusters among surgically treated esophageal cancer patients. Nevertheless, interpretations of results must be made cautiously as statistically derived clusters can be affected by several methodological considerations, and clinical relevance can be difficult to determine. Symptom clusters may vary according to the assessment of symptoms, the prevalence of symptoms in the sample, sample size and composition.[13] In addition, the symptoms reported by patients were recoded into binary variables to estimate the extent of the presence or absence of a symptom based on the proportion of patients responding "quite a bit" and "very much" (i.e. symptom present) versus "not at all" and "a little" (i.e. symptom absent) to the symptom items in the questionnaires. Categorizing symptoms as present or absent addresses only one dimension of symptom experience; that is, symptom frequency. However, this categorization describing the proportion of patients experiencing a symptom based on responses of "very much" or "quite a bit" to items on the EORTC QLQ-C30 was used previously in symptom clusters research among cancer patients.[27] Further, it is difficult to determine whether the symptom clusters identified in this study are stable long-term clusters. However, the assessment of symptoms at six months

following surgery was based on previous research suggesting that by this point the acute postoperative phase has subsided, and HRQOL and symptom levels have generally returned to a preoperative baseline value in the majority of patients.[8, 31] Nevertheless, it would be of value to test the cluster solution on data obtained at different time points.

There are two conceptual approaches to symptom clusters research, one involving the identification of symptom clusters in patients, and the other the identification of different sub-groups of patients based on their similar symptom profiles.[10] In line with the methodology of one previous study of symptom clusters in advanced cancer, we clustered symptoms reported at six months; subsequently, the symptom cluster was considered present if patients reported at least 50% of symptoms within the symptom cluster.[13] It is important to note that the use of these arbitrary cut-offs to determine cluster membership may have affected the clusters. However, the clinical importance of the symptom clusters identified in the present study is supported by the finding of an association between the presence of symptom clusters among patients and survival duration, independent of other prognostic factors.

Although symptom clusters have not been assessed previously in this group of patients, findings from previous prognostic studies of individual symptoms and functions resonate well with the results of the present study. We identified a cluster characterized largely by symptoms related to aspects of eating (the ED symptom cluster). Both pre- and post-treatment appetite loss[15-17, 22] and dysphagia[22] have previously been identified as independent predictors of increased mortality among surgically treated esophageal cancer patients. Similarly, reflux has been shown to predict mortality among these patients.[18] We also found that presence of the RC symptom cluster, characterized by reflux, dry mouth, problems with taste, and coughing, significantly predicted mortality. We identified a cluster largely composed of symptoms related to pain and fatigue (the FP symptom cluster) that was

associated with an increased risk of mortality (HR 1.2, CI 0.9-1.6). Although this association was not statistically significant, this is in line with previous studies which have found that the individual symptoms of pain and fatigue predict survival independently of a range of known prognostic factors among these patients (HRs ranging from 1.10 to 1.65).[18-20;22]

Due to the poor post-operative prognosis for esophageal cancer patients [3], it is of utmost importance to further the understanding of factors related to prognosis. Previous research on the prognostic impact of symptoms has focused largely on the adverse impact on outcomes of individual symptoms. However, symptoms seldom occur in isolation, and this is the first study to date evaluating the prognostic role of symptom clusters in this patient population. Results from this study have potentially important implications for clinical practice. From a clinical perspective, targeting the symptoms in the ED and RC symptom clusters may be particularly important. It has been suggested that the most prevalent symptom within a symptom cluster may be an indicator for the presence of that particular symptom cluster. Thus targeting the most prevalent symptom in a symptom cluster may contribute to the streamlined assessment and management of symptoms to improve outcomes.[32, 33] Should these results be confirmed in other studies, the findings may be used in clinical practice to direct additional investigations and symptom management strategies in patients who have undergone surgery for esophageal cancer.

In conclusion, symptoms experienced by surgically treated esophageal cancer patients at six months post surgery appear to cluster together, and these clusters have strong prognostic value. If confirmed in future studies, these findings may have clinical relevance for the prediction of prognosis and planning of the follow-up care of these patients after surgery.

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Author contributions

AW and PL designed the study. AJ performed the data analyses and contributed to the interpretation of results and drafting of the manuscript. AW and PL contributed to interpretation of results and drafted the paper. All authors read and approved the final manuscript.

Role of the funding source

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The funders do not bear any responsibility for the analyses or interpretations presented here.

Conflicts of interest

The authors declare that no conflicts of interest exist.

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Figure legends

Figure 1.

Five-year survival in months according to the symptom clusters identified (fatigue/pain (a), reflux/cough (b), eating difficulties (c)), presented as Kaplan-Meier curves for patients with presence *versus* absence of these symptom clusters at six months following surgery for esophageal cancer.

Table 1. Baseline socio-demographic and clinical characteristics for the total sample of surgically treated esophageal cancer patients reporting symptoms at six months and for the symptom clusters identified

Characteristic, *n* (%)	Total	Symptom clusters					
		Fatigue/pain		Reflux/cough		Eating difficulties	
	(*n*=402)	Present (*n*=122)	Absent (*n*=280)	Present (*n*=107)	Absent (*n*=295)	Present (*n*=112)	Absent (*n*=290)
Age							
<60	101 (25)	40 (33)	61 (22)	19 (18)	82 (28)	28 (25)	73 (25)
60-74	232 (58)	60 (49)	172 (61)	71 (66)	161 (55)	64 (57)	168 (58)
>74	69 (17)	22 (18)	47 (17)	17 (16)	52 (18)	20 (18)	49 (17)
Sex							
Female	75 (19)	24 (20)	51 (18)	24 (22)	51 (17)	23 (21)	52 (18)
Male	327 (81)	98 (80)	229 (82)	83 (78)	244 (83)	89 (79)	238 (82)
Tumor stage[a]							
0-I	84 (21)	17 (14)	67 (24)	19 (18)	65 (22)	15 (13)	69 (24)
II	120 (30)	32 (27)	88 (32)	31 (29)	89 (31)	29 (26)	91 (32)
III	161 (41)	60 (50)	101 (36)	51 (48)	110 (38)	59 (53)	102 (36)
IV	33 (8)	11 (9)	22 (8)	6 (6)	27 (9)	9 (8)	24 (8)
Tumor histology							
Squamous cell carcinoma	98 (24)	42 (34)	56 (20)	38 (36)	60 (20)	34 (30)	64 (22)
Adenocarcinoma	304 (76)	80 (66)	224 (80)	69 (64)	235 (80)	78 (70)	226 (78)
Type of operation[b]							
Esophageal resection	302 (76)	96 (79)	206 (74)	87 (81)	215 (73)	89 (79)	213 (74)
Cardia resection	17 (4)	3 (2)	14 (5)	2 (2)	15 (5)	1 (1)	16 (6)
Extended total gastrectomy	41 (10)	11 (9)	30 (11)	10 (9)	31 (11)	12 (11)	29 (10)
Total gastrectomy and esophageal resection	40 (10)	12 (10)	28 (10)	8 (7)	32 (11)	10 (9)	30 (10
Complications							
0	269 (67)	67 (55)	202 (72)	59 (55)	210 (71)	63 (56)	206 (71)
1	89 (22)	35 (29)	54 (19)	32 (30)	57 (19)	31 (28)	58 (20)
>1	44 (11)	29 (16)	24 (9)	16 (15)	28 (9)	18 (16)	26 (9)
Co-morbidity							
0	164 (41)	45 (37)	119 (43)	42 (39)	122 (41)	44 (39)	120 (41)
≥1	238 (59)	77 (63)	161 (57)	65 (61)	173 (59)	68 (61)	170 (59)

n number, [a]Missing *n*=4, [b]Missing *n*=2.