

Title: Medical and surgical complications and health-related quality of life after esophageal cancer surgery.

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Running head: Types of complications and HRQOL

Mini-Abstract

Medical and surgical complications were assessed in relation to HRQOL in a prospective nationwide population-based Swedish esophageal cancer surgery cohort of 616 patients.

Medical complications were associated with long-lasting impairments and worsening HRQOL, while the negative effects of surgical complications on HRQOL seemed to minimize after 5 years post-surgery.

Abstract

Objective: To evaluate the impact of postoperative medical and surgical complications on health-related quality of life (HRQOL) in esophageal cancer.

Background: Complications after esophageal surgery negatively affect HRQOL, but it is unclear whether medical and surgical complications differ in effects.

Methods: This Swedish population-based, nationwide and prospective cohort study enrolled 616 patients undergoing esophageal cancer surgery during 2001-2005, with 10 years of follow-up. The exposure was the occurrence of the predefined postoperative medical or surgical technical complications. The study outcome was HRQOL, evaluated by EORTC questionnaires at 6 months, 3, 5 and 10 years after surgery. Linear mixed models, adjusted for confounders and complications, provided mean score differences (MD) and 95% confidence intervals (CI) for each HRQOL scale and item.

Results: Of the 616 patients, 217 (35%) had medical and 163 (26%) had surgical postoperative complications. In patients with medical complications, HRQOL was generally worse at all time points, with worse global quality of life (QOL) (MD -10, 95% CI -18 to -2) and dyspnea (MD 16, 95% CI 5 to 27) from 3 years onwards, compared to those without. Patients with surgical complications had worse HRQOL outcomes up to 5 years after surgery, e.g., dyspnea at 6 months (MD 11, 95% CI 4 to 19) and global QOL at 3 years (MD -13 -22 to -5), than those without.

Conclusion: Medical complications are associated with long-lasting impairments and worsening HRQOL, while the negative effects of surgical complications on HRQOL seem to minimize after 5 years post-surgery.

Keywords: Esophagus; neoplasm; complications; quality of life; survivorship.

Introduction

The surgical treatment of esophageal cancer is characterized by poor prognosis and high incidence of complications.^{1,2} Curatively intended surgery carries a 30-55% 5-year survival and 40% complication rate³⁻⁶ resulting in poor post-operative health-related quality of life (HRQOL).⁷⁻⁹ Major complications during treatment increase the risk of deterioration of HRQOL in the short- and long term,¹⁰⁻¹⁴ and complications and poor HRQOL are poor prognostic risk factors.^{15,16} Complications can be divided in those related to surgery, such as major bleeding or anastomotic leakage, and to medical, such as sepsis or myocardial infarction. Surgical complications could be potentially reduced by improving surgeon volume and education,^{3,17,18} whereas medical complications could be avoided by, for example, optimization of the patients before surgery and improving perioperative care.¹⁹ The long-term effects of, and the difference between medical and surgical complications after surgery in esophageal cancer patients are unknown.

It was hypothesized that especially medical, but also surgical complications relate to poor recovery of HRQOL in the long term. The main aim of the study was to examine the impact of medical and surgical complications on HRQOL from 6 months to 10 years after esophageal cancer surgery.

Methods

Study design

A nationwide Swedish, population-based, and prospective cohort study was conducted, and 616 patients surgically treated for esophageal or gastroesophageal junction (GEJ) cancer in Sweden were recruited between April 2, 2001 and December 31, 2005, representing 90% of all patients undergoing esophageal cancer surgery during that period.⁹ Prospectively collected variables included patient characteristics, tumor characteristics, surgical treatment and predefined complications occurring within 30 days of surgery. Using the immutable personal identity numbers assigned to all residents in Sweden,²⁰ the study patients were linked to the Patient Registry and the Cancer Registry for information on co-morbidities²¹ and the Swedish Registry of the Total Population for retrieval of survival data. The information in these registries is nearly 100% complete.^{22,23} The study was approved by the Regional Ethical Review Board in Stockholm, Sweden and all participating patients gave informed consent.

Exposure

There were two exposures: the occurrence of any of the predefined 1) medical complications (yes or no), and 2) surgical complications (yes or no) within 30 days of surgery. These complications were predefined by a group of experienced esophageal cancer surgeons in Sweden before the data collection.

Medical complications were defined as: 1) sepsis (clinical symptoms and positive bacterial culture in the blood), 2) pneumonia (clinical symptoms and radiologically verified), 3) acute liver insufficiency (progressive or permanent), 4) acute renal failure (need of dialysis), 5) deep vein thrombosis (radiologically verified), 6) pulmonary embolism (radiologically verified), 7) myocardial infarction (verified with electrocardiogram or heart enzymes), 8) atrial fibrillation (newly diagnosed by ECG and needs treatment), 9) stroke (radiologically

verified), 10) respiratory failure (intubation or mechanical ventilation), and 11) pulmonary edema (newly diagnosed, radiologically verified, symptomatic and needing treatment). Surgical complications included: 1) major postoperative bleeding (exceeding 2000 ml or requiring reoperation), 2) splenectomy (after failure of other methods of hemostasis), 3) anastomotic insufficiency (clinically and radiologically verified), 4) necrosis of the substitute (clinically significant ischemia with perforation or ulceration), 5) severe lymph leakage (drainage >7 days or reoperation), 6) gastric perforation (postoperatively identified leakage from the gastric tube), 7) esophago-tracheal fistula (radiologically and clinically verified, requiring treatment), 8) empyema (radiologically or surgically verified collection of pus at least 3 cm in diameter with symptoms of fever, pain or dyspnea), 9) intra-abdominal abscess (criteria as in empyema), 10) wound infection (symptomatic collection of pus in the wound, requiring treatment), 11) wound rupture (clinically obvious dehiscence, requiring reoperation), and 12) bowel obstruction (radiologically verified, demanding surgery).

Outcomes

The outcome of the study was HRQOL. Measurement of HRQOL was completed at 6 months, 3, 5 and 10 years after surgery using mailed, self-administered questionnaires, developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC). The patients received up to three reminders if they did not respond.

The 30-item core questionnaire (QLQ-C30) has 9 multi-item scales measuring global quality of life (QOL), functions (physical, role, cognitive, emotional and social functioning) and symptoms (fatigue, pain, and nausea and vomiting), and 6 single items measuring general cancer symptoms (dyspnea, appetite loss, insomnia, constipation, diarrhea) and financial impact.²⁴ Esophageal-specific symptoms are measured with the supplemental module QLQ-

OES18, which comprises 4 symptom scales (eating, reflux, esophageal pain, and dysphagia) and 6 single items (cough, dry mouth, taste, choking, speech, and trouble swallowing saliva).

²⁵ Each item (on both questionnaires) has a four-point Likert-scale: 1) “not at all,” 2) “a little,” 3) “quite a bit,” and 4) “very much,” except for the global quality-of-life scale, which has seven response alternatives ranging from “very poor” to “excellent.” The responses were linearly transformed into scores on a 0 to 100 scale. In functions, greater numbers mean better function, while in the symptoms scales and items greater numbers mean worse symptoms. Missing data were handled according to questionnaire developers’ recommendations.

Statistical methods

All data management and statistical analyses were conducted by a senior biostatistician with expertise in HRQOL analyses (A.J.). Linear mixed-effects models were used to calculate mean score differences (MD) with 95% confidence intervals (CI) between groups and adjust for confounding factors for each scale and item.

The following potential confounding factors were adjusted for: 1) pre-diagnosis HRQOL score for each scale and item, 2) age: <60 or ≥60 years (longitudinally adjusted), 3) sex: male or female, 4) Charlson’s comorbidity index: 0, 1 or ≥2, 5) histology: squamous-cell carcinoma or adenocarcinoma, 6) tumor stage: 0-I or II-IV, 7) annual surgeon volume: 0-6 per year or >6 per year, and 8) mutual adjustment for medical (yes or no) and surgical complications (yes or no) as some of the patients have had both surgical and medical complications.

To compare the HRQOL to pre-diagnosis HRQOL, and to take into account the changes in HRQOL due to ageing and potentially increasing comorbidity during the long follow-up, HRQOL in the Swedish background population was used as a proxy pre-diagnosis score. Therefore, a random sample of 4,910 people (70.5% response rate) in the Swedish background population for both HRQOL questionnaires were used as reference HRQOL

scores for adjustments,^{26,27} matched by sex, changes in comorbidities, education level, and age over time (i.e. a 60-year old patient is compared to four matched 60-year old patients at 6 months and to four 70-year old patients at 10 years). The adjustment for comorbidities was done separately at each time point, with comorbidity data corresponding to the time point in focus in the analysis. Registries provided comorbidity data for up to five years. The self-reported comorbidity at 10 years was categorized according to Charlson's comorbidity index and new comorbidities were added to corresponding 5-year comorbidity categories for each patient.

The clinical relevance of the differences in HRQOL scores was determined using the evidence-based interpretation guidelines for the QLQ-C30 subscales, which were different for cross-sectional (between the exposure groups),²⁸ and between time points.²⁹ If no established cut-offs were available, an MD of 10–20 points were considered a moderate difference and ≥ 20 points a large difference.^{30,31} Only moderate and large changes were considered clinically relevant and further tested for statistical significance using T-test. Missing values were dealt with by complete case analysis. SAS version 9.4 (Cary, NC) was used for all statistical analyses.

Results

Patients

A total of 616 patients underwent open surgical resection for esophageal cancer during the study period and were included in the study. Of these patients, 506 (82%) were alive and 402 (79%) of them completed the questionnaires at 6 months. At 3 years there were 211 (34%) patients alive with 178 (84%) returning the questionnaires. At 5 years, 153 (25%) patients were alive, of whom 141 (92%) completed the questionnaires. At 10 years, 104 (17%) were alive and 92 (88%) responded to the questionnaires.

There were more early-stage tumors in the 10-year responders' group than in the baseline characteristics of the total cohort. Patients' characteristics at the time of surgery (baseline) and at 10 years follow-up are described in Table 1. Of the 616 patients undergoing surgery, 299 (49%) experienced at least one of the predefined complications. In total, 217 (35%) of the patients had medical complications and 163 (26%) had surgical complications. Of the responders at 10 years, 37 (40%) had had at least one postoperative complication, of whom 28 (30%) had medical and 21 (23%) had surgical complications (Table 2).

Medical complications and general quality of life, functions and symptoms

The HRQOL scales and items for the QLQ-C30 and the QLQ-OES18 for each time point are presented in Table 3. In patients with medical complications, the global QOL was significantly worse from 3 years after surgery and onwards, compared to those without medical complications (MD -10, 95% CI -18 to -2 at 3 years and MD -14, 95% CI -24 to -4 at 10 years).

For functional scales, patients with medical complications had generally worse scores for all scales at all time points compared to those without medical complications. The differences

were clinically and statistically significant for physical function at 10 years (MD -14, 95% CI -23 to -5), emotional function at 5 years (MD -12, 95% CI -22 to -3) and social function at 10 years after surgery (MD -13, 95% CI -26 to -1).

A similar pattern was seen for the symptom scales and single items where patients with medical complications also reported generally worse scores throughout the follow-up period. There was a large clinical and statistically significant difference in dyspnea at the 3, 5 and 10-year time points with worse symptoms in patients experiencing medical complications (MD 16, 95% CI 5 to 27 at 3 years and MD 22, 95% CI 9 to 36 at 10 years). For other symptoms scales and single items, the differences at 6 months, 3 years and 5 years were not clinically significant. At 10 years, all symptoms scales and single items except insomnia and constipation were clinically and statistically significantly worse in patients experiencing medical complications compared to those who did not.

For the QLQ-OES18 questionnaires, those patients with medical complications had significantly more eating restrictions (MD 13, 95% CI 2 to 24) and esophageal pain (MD 17, 95% CI 7 to 28) at 10 years, more problems with taste from 6 months to 5 years (MD 11, 95% CI 5 to 18 at 6 months and MD 13, 95% CI 1 to 26 at 5 years) and more choking symptoms at 10 years (MD 14, 95% CI 2 to 25) compared to those without medical complications. For the QLQ-OES18 questionnaires, no other significant differences were observed between the groups.

Surgical complications and general quality of life, functions and symptoms

The HRQOL scales and items for the QLQ-C30 and the QLQ-OES18 for each time point are presented in Table 4. In patients with surgical complications, the global QOL was clinically and statistically significantly worse at 3 years (MD -13, 95% CI -22 to -5) and 5 years after surgery (MD -13, 95% CI -24 to -3), compared to those without surgical complications.

For functional scales, patients with surgical complications reported generally worse scores for all scales at all time points compared to those without, but the differences did not reach the clinically significant level.

For the symptoms scales and single items in the QLQ-C30 questionnaire, patients with surgical complications had generally worse scores compared to those without surgical complications. Fatigue at 3 years after surgery (MD 15, 95% CI 4 to 25), nausea and vomiting at 6 months to 5 years after surgery (MD 12, 95% CI 7 to 18 at 6 months and MD 11, 95% CI 0 to 22 at 5 years), dyspnea at 6 months to 3 years after surgery (MD 11, 95% CI 4 to 19 at 6 months and MD 12, 95% CI 0 to 24 at 3 years), and appetite at 3 years after surgery (MD 20, 95% CI 6 to 33), were clinically and statistically significantly worse in those who had surgical complications. For other symptom scales and single items there were no clinically significant differences between the groups.

Regarding the QLQ-OES18 questionnaire, Patients with surgical complications had clinically and statistically significantly more eating restrictions (MD 10, 95% CI 0 to 20) and dysphagia (MD 11, 95% CI 2 to 21) at 3 years, cough from 6 months to 3 years (MD 16, 95% CI 9 to 24 at 6 months and MD 13, 95% CI 1 to 25 at 3 years), and choking from 3 years to 5 years (MD 13, 95% CI 3 to 23 at 3 years and MD 13, 95% CI 1 to 25 at 5 years). No other significant differences were observed between the groups for the QLQ-OES18 questionnaire.

Discussion

In this population-based prospective cohort study of patients undergoing esophageal cancer surgery, postoperative medical complications were independently associated with poor and worsening HRQOL on a 10-year trajectory, while surgical complications were associated with poor HRQOL up to 5 years postoperatively.

There are some strengths and weaknesses in the present study that should be discussed before interpreting the results. The prospective, population-based and longitudinal design of this study counteracts selection bias and recall bias. Further, the large sample size, complete follow-up and high questionnaire response rates (78% - 92%) at each time point ensure statistical power and clinically meaningful conclusions. Non-participation might have caused some selection bias, especially at 6 months, but the results were highly similar at 6 months, 3 and 5 years, alleviating this concern. The longitudinal adjustment for HRQOL in the background population, and not the true baseline HRQOL in the patients, reduces the effects of post-diagnostic emotional affection, disease symptoms and effects of neoadjuvant treatment on HRQOL. Therefore, the background population better reflects the pre-diagnosis HRQOL, and takes into account aging-related changes in HRQOL of the general population in the long follow-up. Longitudinal adjustment for comorbidities alleviates the effects of newly acquired comorbidities during long follow-up. Information bias is reduced by using well-validated questionnaires. The patients' perception of HRQOL over time by recalibration of their personal standards, reprioritization of their personal values, and reconceptualization of their quality of life,³² might be considered a potential limitation of the study. However, this response shift effect would be similar in both the exposed and non-exposed group of patients. Furthermore, the evidence-based guidelines that take these changes into account were used for interpretation of clinical relevance of changes, which further reduced the challenges

associated with potential multiple testing. Another potential limitation of the present study is the dichotomization of complications to medical and surgical, as for example sepsis could be a result of primary infection or alternatively related to a surgical complication such as anastomotic leak or abscess. Likewise, anastomotic leak could lead to a multitude of medical complications, including multi-organ failure, causing some overlap between the groups. Since all patients having both types of complications were included in both medical and surgical complications groups, and complications were mutually adjusted for in the analysis (medical complications were adjusted for in the analysis of surgical complications and vice versa), the resulting effect of potential misclassification should be reduced to an acceptable level. This potential mixed pattern of cause-effect should however be considered when interpreting the results.

Our previous study suggested impaired and worsening HRQOL over time for those with postoperative complications up to 10 years after esophageal cancer surgery.¹⁴ However, the effects of postoperative medical and surgical complications on HRQOL were unknown in the long term, prompting the current study. A previous Swedish study suggested that technical surgical complications during esophageal cancer surgery are associated with poor global HRQOL, physical and role functions, fatigue, nausea and vomiting, dyspnea and coughing at 6 months after surgery.¹¹ Another Swedish study showed that anastomotic leak during esophageal cancer surgery increased risk of eating difficulties at 6 months and 3 years, compared to those without anastomotic leak.¹³ An Italian study suggested that postoperative complications were associated with poor global quality of life at 6-12 months.¹² The results of the present study show that medical complications, when adjusted for confounders and surgical complications, are associated with considerably impaired global quality of life and dyspnea from 3 years onwards, as well as a multitude of symptoms in the 5 and 10 year

follow-up, while surgical complications are associated with poor global HRQOL until 5 years, and symptoms, most importantly fatigue, nausea and vomiting, dyspnea, and problems related to eating or swallowing until 3 to 5 years.

Patients with lower lung function and lower performance status, and those with higher serum creatinine are prone to pulmonary complications after esophagectomy.^{33,34} In the present study, pulmonary complications including pneumonia and respiratory failure were among the most common medical complications. Therefore, it is not surprising that global HRQOL and dyspnea were among the most profoundly affected areas in HRQOL measurements over time. These conditions predisposing patients to medical complications are long-term illnesses that progress over time and might be reflected at 10 years after surgery even after adjustment for comorbidities and HRQOL of the general population.

Prognostic nutritional index and preoperatively abnormal pulse might predict severe postoperative complications.³⁵ Smoking,³⁶ heart failure, hypertension and renal insufficiency are associated with anastomotic leak after esophagectomy.³⁷ Anastomotic problems and surgical infections were the dominant surgical complications. It is biologically plausible that these complications, i.e. surgical infections and problems including reoperations in the surgical field are associated with problems related to fatigue, gastrointestinal symptoms, problems in eating, swallowing and coughing, and result in poor HRQOL. However, the HRQOL in patients with surgical complications improved between 5 and 10 years of follow-up, suggesting that these surgical complications heal in the long term and associated symptoms get better over the course of 5 to 10 years.

The proportion of esophageal cancer patients surviving at least 5 years postoperatively is increasing.^{6,38} This, together with high incidence of complications during surgery³⁹ signifies that prevention of complications and treatment of complication-related problems in HRQOL are becoming increasingly important. Careful selection of patients for surgery, cardiopulmonary optimization and smoking cessation⁴⁰ could reduce medical complications. Minimally invasive surgery might reduce pulmonary complications.^{41,42} For surgical complications, centralization of esophageal cancer surgery to high volume surgeons,³ as well as mentorship programs for surgeons might be effective for preventing surgical complications. For those patients who have sustained postoperative complications physical and psychological rehabilitation programs are encouraged, together with information on the prognosis of HRQOL over time provided in the present study. To further dissect the effects of each individual complication on patients' lives, further studies focusing on complications and respective function and symptom domains are needed.

In conclusion, this prospective, population-based cohort study shows that occurrence of postoperative medical complications is associated with worsening HRQOL outcomes up to 10 years after surgery, while surgical complications are associated with poor HRQOL outcomes up to 3 to 5 years after surgery, highlighting the need for tailored and long-term follow-up in a multidisciplinary setting. The results further encourage actions to prevent complications, promote research on the effects of specific complications and interventions on patients' HRQOL, and provide information on the complication-related HRQOL over time for physicians and patients.

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Table 1. Baseline demographics of the 616 patients in the cohort, and the clinical characteristics of 92 patients surviving 10 years after esophageal cancer surgery who had medical or surgical postoperative complications, or not.

	Baseline <i>n</i> = 616			Responders at 10 years <i>n</i> = 92		
	No complications Number (%)	Medical complications Number (%)*	Surgical complications Number (%)*	No complications Number (%)	Medical complications Number (%)*	Surgical complications Number (%)*
Total number	317 (51)	217 (35)	163 (26)	55 (60)	28 (30)	21 (23)
Age, median [IQR]	67 [60 - 73]	69 [62 - 74]	66 [59 - 73]	73 [68 - 80]	68 [69 – 81]	72 [69 – 80]]
Sex						
Male	259 (82)	175 (81)	133 (82)	40 (73)	25 (89)	18 (86)
Female	58 (18)	42 (19)	30 (18)	15 (27)	3 (11)	3 (14)
Histology						
Adenocarcinoma	248 (78)	161 (74)	117 (72)	43 (78)	21 (75)	19 (90)
Squamous cell	68 (21)	56 (26)	46 (28)	12 (22)	7 (25)	2 (10)
Missing	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tumor stage						
I-II	154 (49)	103 (47)	74 (45)	46 (84)	25 (89)	17 (81)
III-IV	159 (51)	110 (51)	88 (54)	9 (16)	3 (11)	4 (19)
Missing	4 (1)	4 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Charlson comorbidity score						
0	38 (12)	20 (9)	25 (15)	6 (11)	4 (14)	7 (33)
1	150 (47)	73 (34)	60 (37)	30 (55)	11 (39)	6 (29)
≥2	129 (41)	124 (57)	78 (48)	19 (35)	13 (46)	8 (38)
Annual surgeon volume						
0-6	150 (47)	141 (65)	97 (60)	23 (42)	17 (61)	10 (48)
≥7	167 (53)	76 (35)	66 (40)	32 (58)	11 (39)	11 (52)

IQR, interquartile range. *A patient could have both medical and surgical complications

Table 2. Postoperative complications up to 30 days after surgery in the 616 patients in the total cohort, and in the 92 patients responding to the 10 year questionnaires.

	Baseline n (%)	10 year responders n (%)
Complications*		
No	317 (51)	55 (60)
Medical	217 (35)	28 (30)
Surgical	163 (26)	23 (23)
Type of medical complication*		
Sepsis	54 (9)	8 (9)
Pneumonia	74 (12)	9 (10)
Liver insufficiency	1 (0)	1 (1)
Renal failure	14 (2)	1 (1)
Deep vein thrombosis	6 (1)	1 (1)
Pulmonary embolism	8 (1)	1 (1)
Myocardial infarction	9 (1)	0
Atrial fibrillation	98 (16)	9 (10)
Stroke	5 (1)	1 (1)
Respiratory failure	101 (16)	13 (14)
Pulmonary edema	9 (1)	1 (1)
Type of surgical complication*		
Major bleeding during surgery	16 (3)	1 (1)
Splenectomy	21 (3)	3 (3)
Anastomotic insufficiency	57 (9)	8 (9)
Substitute necrosis	6 (1)	0 (0)
Severe lymph leakage	13 (2)	0 (0)
Gastric perforation	6 (1)	1 (1)
Esophago-tracheal fistula	11 (11)	1 (1)
Empyema	24 (4)	2 (2)
Intra-abdominal abscess	9 (1)	1 (1)
Wound infection	15 (2)	1 (1)
Wound rupture	8 (1)	3 (3)
Bowel obstruction	4 (1)	1 (1)

*Each patient could have more than one type of complication

Table 3. Adjusted mean differences (MD)* with 95% confidence intervals (CI) in health-related quality of life (HRQOL) scores between patients who had and did not have predefined **medical complications** after esophageal cancer surgery until 10 years. Values that are both clinically relevant and statistically significant are bolded.

	Time point of HRQOL measurement and number of patients			
	6 months (n = 402)	3 years (n = 177)	5 years (n = 141)	10 years (n = 92)
Questionnaire scales and items	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)
EORTC QLQ-C30				
Global QOL	-8 (-12 to -3)	-10 (-18 to -2)	-12 (-22 to -3)	-14 (-24 to -4)
Physical function	-4 (-9 to 0)	-7 (-14 to 1)	-7 (-15 to 2)	-14 (-23 to -5)
Role function	-15 (-22 to -7)	-13 (-25 to 0)	-13 (-28 to 2)	0 (-17 to 16)
Emotional function	-5 (-10 to 0)	-8 (-17 to 0)	-12 (-22 to -3)	-9 (-20 to 1)
Cognitive function	-2 (-6 to 3)	-8 (-16 to 0)	-8 (-17 to 1)	-7 (-17 to 2)
Social function	-4 (-9 to 2)	-7 (-17 to 3)	-9 (-21 to 2)	-13 (-26 to -1)
Fatigue	2 (-3 to 8)	7 (-3 to 16)	7 (-4 to 18)	17 (6 to 29)
Nausea / vomiting	4 (-1 to 9)	5 (-3 to 13)	8 (-2 to 17)	14 (4 to 24)
Pain	-3 (-9 to 3)	0 (-10 to 9)	-3 (-14 to 8)	16 (4 to 28)
Dyspnea	8 (1 to 14)	16 (5 to 27)	20 (7 to 32)	22 (9 to 36)
Insomnia	5 (-1 to 12)	1 (-10 to 13)	1 (-13 to 14)	14 (-1 to 29)
Appetite	10 (3 to 18)	11 (-1 to 23)	14 (0 to 28) [#]	22 (7 to 37)
Constipation	8 (3 to 13)	6 (-3 to 14)	6 (-4 to 16)	-4 (-16 to 7)
Diarrhea	-2 (-9 to 5)	6 (-5 to 18)	8 (-5 to 21)	29 (14 to 43)
Financial difficulties	4 (-1 to 10)	4 (-5 to 13)	10 (-1 to 20) [#]	15 (3 to 26)
EORTC QLQ-OES18				
Eating restrictions	7 (2 to 12)	5 (-4 to 14)	9 (-1 to 20)	13 (2 to 24)
Reflux	3 (-3 to 10)	3 (-7 to 14)	11 (-1 to 23)	0 (-13 to 13)
Esophageal pain	1 (-4 to 6)	-3 (-12 to 5)	-1 (-10 to 9)	17 (7 to 28)
Dysphagia	4 (-2 to 9)	-2 (-11 to 7)	1 (-9 to 12)	-2 (-13 to 9)
Cough	2 (-5 to 8)	0 (-11 to 11)	-3 (-15 to 10)	10 (-4 to 24)
Dry mouth	7 (0 to 13)	9 (-2 to 20)	7 (-6 to 20)	8 (-6 to 21)
Taste	11 (5 to 18)	12 (1 to 23)	13 (1 to 26)	8 (-5 to 22)
Choking	5 (-1 to 10)	5 (-4 to 14)	10 (0 to 21)	14 (2 to 25)
Speaking	0 (-5 to 5)	6 (-3 to 15)	-8 (-2 to 18)	7 (-4 to 17)
Swallowing saliva	4 (-2 to 9)	8 (-2 to 17)	4 (-7 to 15)	11 (-1 to 23)

* The MDs are adjusted for HRQOL longitudinally adjusted for age, sex and comorbidities, patient age, sex, comorbidity, tumor stage, histology, surgeon volume and surgical complications. [#] Rounded value, not clinically relevant. QOL= Quality of life.

Table 4. Adjusted mean differences (MD)* with 95% confidence intervals (CI) in health-related quality of life (HRQOL) scores between patients that had and did not have predefined **surgical complications** after esophageal cancer surgery until 10 years. Values that are both clinically relevant and statistically significant are bolded.

	Time point of HRQOL measurement and number of patients			
	6 months (n = 402)	3 years (n = 177)	5 years (n =141)	10 years (n = 92)
Questionnaire scales and items	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)
EORTC QLQ-C30				
Global QOL	-9 (-14 to -4)	-13 (-22 to -5)	-13 (-24 to -3)	4 (-8 to 15)
Physical function	-10 (-15 to -5)	-9 (-17 to -1)	-9 (-19 to 0)	-5 (-15 to 6)
Role function	-15 (-22 to -7)	-13 (-25 to 0)	-13 (-28 to 2)	0 (-17 to 16)
Emotional function	-3 (-8 to 3)	-2 (-11 to 7)	-3 (-14 to 7)	2 (-10 to 14)
Cognitive function	-2 (-7 to 3)	-1 (-9 to 7)	-3 (-13 to 7)	-9 (-20 to 2)
Social function	-6 (-12 to 1)	-2 (-13 to 8)	-3 (-15 to 10)	2 (-13 to 16)
Fatigue	11 (5 to 18)	15 (4 to 25)	13 (1 to 25)#	3 (-10 to 17)
Nausea / vomiting	12 (7 to 18)	12 (3 to 22)	11 (0 to 22)	2 (-10 to 14)
Pain	6 (-1 to 13)	11 (0 to 22)	13 (0 to 26)#	10 (-5 to 24)
Dyspnea	11 (4 to 19)	12 (0 to 24)	4 (-10 to 18)	10 (-6 to 26)
Insomnia	5 (-1 to 12)	1 (-10 to 13)	1 (-13 to 14)	14 (-1 to 29)
Appetite	11 (3 to 20)	20 (6 to 33)	14 (-2 to 30)	-7 (-24 to 11)
Constipation	8 (3 to 13)	6 (-3 to 14)	6 (-4 to 16)	-4 (-16 to 7)
Diarrhea	1 (-7 to 9)	-3 (-16 to 9)	-6 (-21 to 9)	-6 (-23 to 10)
Financial difficulties	2 (-4 to 8)	0 (-10 to 10)	-3 (-15 to 9)	3 (-11 to 16)
EORTC QLQ-OES18				
Eating restrictions	6 (0 to 12)	10 (0 to 20)	7 (-4 to 19)	8 (-5 to 21)
Reflux	1 (-6 to 8)	-2 (-13 to 10)	-10 (-24 to 3)	2 (-13 to 17)
Esophageal pain	1 (-5 to 7)	6 (-4 to 15)	0 (-11 to 11)	-3 (-15 to 9)
Dysphagia	6 (0 to 12)	11 (2 to 21)	4 (-7 to 16)	2 (-11 to 15)
Cough	16 (9 to 24)	13 (1 to 25)	14 (0 to 28)	0 (-16 to 16)
Dry mouth	-5 (-12 to 2)	-11 (-23 to 1)	-11 (-26 to 3)	3 (-13 to 18)
Taste	1 (-6 to 8)	0 (-11 to 12)	-5 (-19 to 9)	0 (-16 to 16)
Choking	9 (3 to 15)	13 (3 to 23)	13 (1 to 25)	11 (-3 to 25)
Speaking	9 (4 to 15)	5 (-4 to 14)	1 (-11 to 12)	3 (-9 to 16)
Swallowing saliva	2 (-4 to 9)	-5 (-15 to 6)	-4 (-16 to 9)	6 (-7 to 20)

* The MDs are adjusted for HRQOL longitudinally adjusted for age, sex and comorbidities, patient age, sex, comorbidity, tumor stage, histology, surgeon volume and surgical complications. #Rounded value, not clinically relevant. QOL= Quality of life.