

**Title: Postoperative complications and health-related quality of life 10 years after esophageal cancer surgery.**

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**Running head:** Postoperative complications and HRQOL

## **Mini-Abstract**

Complications were analyzed in relation to 10-year HRQOL in a prospective nationwide population-based Swedish cohort of 616 patients undergoing open esophageal cancer surgery, HRQOL was impaired after complications on twelve of the 25 scales and items measured at 10-year follow-up, including physical function, fatigue, pain, dyspnea, insomnia and eating problems.

## **Abstract**

**Objective:** To evaluate the impact of postoperative complications on health-related quality of life (HRQOL) up to 10 years after surgery for esophageal cancer.

**Summary Background Data:** The impact of postoperative complications on HRQOL past 5 years is unknown.

**Methods:** Some 616 patients undergoing open esophageal cancer surgery between April 2, 2001 and December 31, 2005 in Sweden were enrolled in this population-based, nationwide and prospective cohort study. Exposure was the occurrence of predefined postoperative complications, and the outcome was HRQOL evaluated by validated EORTC questionnaires at 6 months, 3, 5 and 10 years after surgery. Linear mixed models, adjusted for longitudinal HRQOL in the general population and confounders, provided mean score differences (MD) with 95% confidence intervals (CI) for each HRQOL item and scale in patients with or without postoperative complications.

**Results:** At 10 years, 104 (17%) patients were alive and 92 (88%) answered the HRQOL questionnaires. Of these, 37 (40%) had at least one predefined postoperative complication. Twelve of the 25 scales and items were significantly worse in patients with postoperative complications 10 years after surgery, e.g., physical function (MD -15, 95% CI -24 to -7), fatigue (MD 16, 95% CI 5 to 26), pain (MD 18, 95% CI 7 to 30), dyspnea (MD 15, 95% CI 2 to 27), insomnia (MD 20, 95% CI 8 to 32) and eating problems (MD 14, 95% CI 3 to 24) compared to patients without complications.

**Conclusions:** Postoperative complications are associated with considerably impaired HRQOL up to 10 years after esophageal cancer surgery.

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

## **Introduction**

Esophageal cancer, the 6<sup>th</sup> most common cause of cancer death globally, is characterized by increasing incidence, demanding treatment and poor prognosis.<sup>1,2</sup> The 5-year survival is around 30-55% in patients eligible for curative treatment, and the risk of surgery-related complications is over 40%.<sup>3-5</sup> The life of the patient after esophageal cancer surgery is generally characterized by poor health-related quality of life (HRQOL).<sup>6-8</sup> Major complications during treatment are known to cause deterioration of HRQOL in the short- but also in the long term.<sup>9-12</sup> Moreover, complications and poor postoperative HRQOL are known risk factors for poor prognosis.<sup>13,14</sup> The impact of complications on 10-year HRQOL is thus far not known.

We hypothesized that complications relate to poor recovery of HRQOL over time and poor HRQOL also at 10 years after esophageal cancer surgery. The main aim of the study was to examine the impact of complications on HRQOL at 10 years after surgery. The secondary aim was to elucidate the HRQOL trajectory in relation to complications from 6 months to 10 years postoperatively.

## **Methods**

### *Study design*

A nationwide Swedish, population-based, and prospective cohort study was conducted, entitled the Swedish Esophageal and Cardia Cancer study (SECC).<sup>8</sup> SECC includes 616 patients, representing 90% of all patients operated with curative intent for oesophageal or gastroesophageal junctional (GEJ) cancer in Sweden between April 2, 2001 and December 31, 2005. All patients in the cohort underwent open surgery, with majority operated by transthoracic Ivor-Lewis esophagectomy. No minimally invasive surgeries were done during the study period. Details about all study variables were prospectively assessed and reviewed by the researchers according to a predefined study protocol to ensure uniformity, including patient characteristics (age, sex), tumour characteristics (stage, histology), surgical treatment and predefined complications occurring within 30 days of surgery. SECC is linked to the Patient Registry and the Cancer Registry for information on co-morbidities. Moreover, survival data was obtained from the 100% complete Swedish Registry of the Total Population. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. All participating patients gave informed consent.

### *Exposure*

The main exposure of the study was complications occurring within 30 days of surgery (yes/no). The complications were predefined by a group of experienced esophageal cancer surgeons and researchers, and 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 (requiring drainage for more than 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 (radiologically or surgically verified collection of pus at least 3 cm in diameter with clinical symptoms of fever and pain), 10) wound infection (symptomatic collection of pus in the wound, requiring treatment), 11) wound rupture (clinically obvious dehiscence, requiring reoperation), 12) bowel obstruction (radiologically verified, demanding surgery), 13) sepsis (which caused clinical symptoms and positive bacterial culture in the blood), 14) pneumonia (which caused clinical symptoms and was radiologically verified), 15) liver insufficiency (progressive or permanent), 16) renal failure (in need of dialysis), 17) deep vein thrombosis (radiologically verified), 18) pulmonary embolism (radiologically verified), 19) myocardial infarction (verified with electrocardiogram or heart enzymes), 20) atrial fibrillation (newly diagnosed by ECG and needing treatment), 21) stroke (radiologically verified), 22) respiratory failure (in need of intubation or mechanical ventilation), and 23) pulmonary edema (newly diagnosed, radiologically verified, symptomatic and needing treatment).

### *Outcomes*

The primary outcome of the study was HRQOL. HRQOL was prospectively measured at 6 months, 3, 5, 10 and 15 years (on-going) after surgery using mailed, self-administered questionnaires developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC). Up to three reminders were sent if required. For the purpose of this study, all patients who responded to HRQOL questionnaires at any of the time points were included.

The 30-item core questionnaire (QLQ-C30) has 9 multi-item scales measuring global quality of life, functions (physical, role, emotional, cognitive and social function) and symptoms (fatigue, and nausea and vomiting and pain), and 6 single items measuring general cancer symptoms (dyspnea, insomnia, appetite, constipation, diarrhea) and financial impact.<sup>15</sup> Esophageal-specific symptoms are measured with the supplemental module (QLQ-OES18), which comprises 4 symptom scales (eating restrictions, reflux, esophageal pain, and dysphagia) and 6 single items (cough, dry mouth, taste, choking, speaking, and swallowing saliva).<sup>16</sup> 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.” All responses to the HRQOL questionnaires were linearly transformed into scores on a 0 to 100 scale. Missing data on individual items were handled in line with the recommendations from the questionnaire developers.

To mirror the HRQOL before patients were diagnosed with esophageal cancer, HRQOL scores collected from a random sample of 4,910 (70.5% response rate) people in the Swedish background population for both questionnaires were used as reference HRQOL scores for adjustments.<sup>17, 18</sup>

### *Statistical methods*

All data management and statistical analyses were conducted by a senior biostatistician with expertise in HRQOL analyses (A.J.). Linear mixed-effect models were used to calculate relative HRQOL scores and mean score differences (MD) with 95% confidence intervals (CI) between patients with and without postoperative complications. All analyses were adjusted for the following confounding factors: 1) Reference HRQOL score for each scale and item at

each time point, 2) age in years at each time point (continuous variable), 3) sex: male or female, 4) Charlson's comorbidity index: 0, 1 and  $\geq 2$ , 5) histology: squamous-cell carcinoma or adenocarcinoma, 6) tumor stage: 0-I or II-IV, and 7) annual surgeon volume: 0-6 per year or  $>6$  per year. Reference HRQOL scores were created by calculating mean HRQOL scores for individuals in the Swedish background population who responded to the same questionnaires as the patients.<sup>18</sup> All patients were matched by sex, comorbidities, education level, and age over time (i.e. 60-year old patient is matched to a 60-year old person at 6 months and to a 70-year old at the 10-year follow-up) to approximately 90 individuals from the reference population. The adjustment for comorbidities was done separately at each time point for the study patients. Comorbidities at 10 years were not available so the patients' comorbidities at 5-years were used at the 10-year time point. The evidence-based interpretation guidelines were used to determine the clinical relevance of the differences in HRQOL scores for the QLQ-C30 subscales, which are different for cross-sectional (between the exposure groups),<sup>19</sup> and between time points.<sup>20</sup> When no established cut-off values were available, MDs of 10–20 points were considered a moderate clinical difference and  $\geq 20$  points a large clinical difference.<sup>21, 22</sup> Only moderate or large clinical differences between groups or over time were further tested for statistical significance by inspecting the 95% CI. Missing values were dealt with using complete case analysis. All statistical analyses were conducted using SAS version 9.4 (Cary, NC).



## Results

### *Patients*

Some 616 patients underwent open esophageal cancer surgery during the study period and were included in the study. At 6 months, 506 (82%) patients were alive and 402 (79%) of these completed the questionnaires. At 3, 5 and 10 years there were 212 (34%), 153 (25%), 104 (17%) patients alive of whom 178 (84%), 141 (92%) and 92 (88%) responded to the questionnaires, respectively. The characteristics of the total cohort and patients at 10 years were similar and are described in Table 1. The only exception was a larger proportion of early-stage tumors in the 10-year responders' group compared to the total cohort. Types of complications in the total cohort and at 10 years are described in Table 2. In the total cohort, 299 (49%) patients experienced at least one of the predefined complications while 182 (45%), 81 (46%), 62 (44%), 37 (40%) of the responders at 6 months, 3 years, 5 years and 10 years had experienced at least one postoperative complication, respectively (Table 3).

### *General quality of life, functions and symptoms at each follow-up time point*

The HRQOL scales and items for QLQ-C30 at each time point are shown in Table 3. The global HRQOL in patients with at least one predefined complication was clinically significantly worse until 5 years after surgery (MD -15, 95% CI -24 to -7), but was similar to those who had no complications at 10 years (MD -8, 95% CI -17 to 1). For functional scales, patients with complications had clinically and statistically significantly worse physical (MD -15, 95% CI -24 to -7) function compared to patients without complications at 10 years follow-up, but not at other time points. Although the MDs for role and social functioning were -17 and -10 respectively at 10 years follow-up, the differences did not reach the level of clinical significance.<sup>19</sup> Patients with complications experienced clinically relevantly and statistically

significantly more fatigue, pain, dyspnea, insomnia, diarrhea and financial impact 10 years after surgery compared to patients without complications. Nausea/vomiting and dyspnea were clinically relevantly and statistically significantly worse throughout the follow-up trajectory except for at the 10-year follow-up where the difference in nausea/vomiting did not reach the level of statistical significance.

#### *General quality of life, functions and symptoms over time*

Over time, the patients with complications had a clinically relevant deterioration of cognitive function (MD -7, 95% CI -15 to 0, 10 years versus 6 months) with the largest deterioration between the time points of 5 years and 10 years, however, this deterioration did not reach the level of statistical significance. Sleep deteriorated in patients with complications from 5 years to 10 years (MD 21, 95% CI 8 to 33). In patients without complications, the symptoms of diarrhea improved between 5 and 10 years of follow-up (MD -13, 95% CI -25 to -2, 10 years versus 5 years). There were no other clinically relevant changes in function and symptom scales and items over time in the exposure groups.

#### *Esophageal specific symptoms at each time point*

The HRQOL scales and items for QLQ-OES18 at each time point are shown in Table 4. At the 10-year follow up, the patients with complications experienced more eating problems (MD 14, 95% CI 3 to 24), esophageal pain (MD 13, 95% CI 4 to 23), choking (MD 16, 95% CI 2 to 27) and trouble swallowing saliva (MD 12, 95% CI 1 to 23), than patients without complications. Choking was clinically relevantly and statistically significantly worse in patients with complications at 3, 5 and 10-years from surgery.

#### *Esophageal specific symptoms over time*

Generally, patients suffered from several oesophageal cancer specific symptoms independently of experience of complications, where reflux was gradually worsening over time. Esophageal pain improved in patients without complications between 5 and 10 years of follow-up (MD -10, 95% CI -18 to -2). Taste gradually improved to a clinically significant level (MD -14, 95% CI -25 to -3, 10 years versus 6 months) in patients with complications. There were no other clinically relevant changes in esophageal-specific symptoms over time in the exposure groups.

## **Discussion**

In this population-based prospective cohort study of patients undergoing open esophageal cancer surgery, postoperative complications were found to be independently associated with poor HRQOL as late as 10 years after surgery.

The main strength of this study is its prospective, population-based and longitudinal design which counteracts selection bias and recall bias. The sample size was large, with complete follow-up of the vital status via the reliable Swedish registry of the Total Population, and high questionnaire response rates (79-92%) at each time point, ensuring high statistical power and enabling clinically meaningful and robust conclusions. The lack of preoperative HRQOL values could be considered a potential weakness, as the patient groups having and not having complications could have had different HRQOL before surgery. However, obtaining HRQOL data from a patient at the time of treatment would be misleading since patients usually experience disease symptoms and may be emotionally affected by the cancer diagnosis or neoadjuvant treatment. Therefore longitudinal adjustments for the reference HRQOL in background population were conducted to mimic a level of HRQOL that one could expect prior to the cancer diagnosis. The long follow-up and the newly acquired comorbidities could potentially negatively affect the HRQOL of the patients and bias the results, but this effect was mitigated by adjustment for comorbidity status at the time of follow-up. The use of well-validated questionnaires reduces information bias. Another potential limitation of the study is the change of patients' perception of HRQOL over time by recalibration of their personal standards, reprioritization of their personal values, and reconceptualization of their quality of life.<sup>23</sup> However, the evidence-based guidelines that take these changes into account were used for interpretation of clinical relevance of cross-sectional and longitudinal changes, reducing also the challenges associated with potential multiple testing of differences between the

groups and time points. Moreover, such a response shift effect would be similar in both exposure groups.

The influence of postoperative complications on 10-year HRQOL after esophageal cancer surgery was hitherto unknown. Previous studies from Sweden have evaluated postoperative complications from a shorter-term perspective and found that technical surgical complications were associated with impaired HRQOL including several aspects,<sup>10</sup> and that patients with anastomotic leakage were at an risk of eating difficulties and odynophagia.<sup>12</sup> Furthermore, an Italian study showed that postoperative complications were associated with poor global quality of life at 6-12 months.<sup>11</sup> A previous study from our group using the same cohort found that patients with certain major post-operative complications have similar global HRQOL and functions, but suffer from more symptoms until 5 years after surgery, compared to those without these major complications.<sup>9</sup> The results of the present study show that patients with complications have poorer HRQOL and suffer from more symptoms than those without complications still as long as 10 years after surgery.

The reasons for complications causing worse HRQOL are unclear and can only be speculated upon. Patients with postoperative complications experienced relatively more pain and insomnia, as well as more problems eating, esophageal pain and problems swallowing at 10 years after surgery compared to other follow-up points. Postoperative complications prolong the hospital stay and may delay the rehabilitation process, which are important for the patients' recovery in general.<sup>24, 25</sup> Studies of other cancer types suggest that increased physical activity by means of an intervention might increase physical function, reduce fatigue and improve mental wellness in cancer patients.<sup>24</sup> Fatigue,<sup>26, 27</sup> as well as reduced cognitive function,<sup>28, 29</sup> might also be explained by changes in inflammatory activity in the body.

Infections and increased number of thoraco-abdominal surgeries as a result of complications might activate inflammation,<sup>30</sup> or cause long-standing local symptoms, such as pain, dyspnea, problems eating and swallowing, as well as slower recovery of bowel function through surgical trauma and scar formation.<sup>12, 31, 32</sup> It can be also hypothesized that the aging process is accelerated in individuals experiencing complications, or that those experiencing complications were more frail in ways not measurable in the present study at baseline, resulting in also increased aging-related problems at 10 years follow-up. Different complications are likely reflected in different domains of HRQOL questionnaires, for example anastomotic leakage causing difficulties swallowing, or respiratory complications which in turn increase the pulmonary symptoms. During the very long follow-up the distribution of the complications among the surviving patients changed. At the 10-year follow-up there were for example no or few patients with conduit necrosis, severe lymph leakage and esophagotracheal fistulas. Therefore, the effects of other complications on HRQOL scales and items might be greater at 10 years. Future research may focus on the effect of specific complications on related HRQOL domains in more detail. Severity of the complications might also be associated with poor HRQOL outcomes in the long-term due to greater inflammatory response and insult to tissue repair caused by for example single- or multi organ failure. Therefore, it is important to assess the association between Clavien-Dindo complication severity grading<sup>33</sup> and HRQOL in future studies.

The high frequency of complications associated with esophageal surgery,<sup>34</sup> in combination with the rapidly increasing long-term survival of surgically treated esophageal cancer patients,<sup>5, 35</sup> underlines the importance of postoperative HRQOL for esophageal cancer patients. The results of the present study highlight the need for preventive measures of postoperative complications to preserve survivors' HRQOL. Use of, for example, minimally

invasive surgery,<sup>36, 37</sup> and centralization of esophageal cancer surgery to prevent complications,<sup>3</sup> as well as tailored follow-up and physical and psychological rehabilitation programs for patients that have sustained complications are encouraged.

In conclusion, this prospective, population-based cohort study showed that occurrence of postoperative complications is associated with poor HRQOL outcomes up to 10 years after surgery. The results encourage actions to prevent complications and intensive rehabilitation of patients with complications.

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## References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, et al. The Global Burden of Cancer 2013. *JAMA Oncol* 2015; 1(4):505-27.
2. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. *CA Cancer J Clin* 2013; 63(4):232-48.
3. Viklund P, Lindblad M, Lu M, et al. Risk factors for complications after esophageal cancer resection: a prospective population-based study in Sweden. *Ann Surg* 2006; 243(2):204-11.
4. Rutegard M, Charonis K, Lu Y, et al. Population-based esophageal cancer survival after resection without neoadjuvant therapy: an update. *Surgery* 2012; 152(5):903-10.
5. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. *National Cancer Institute. Bethesda, MD* 2017.
6. Jacobs M, Macefield RC, Elbers RG, et al. Meta-analysis shows clinically relevant and long-lasting deterioration in health-related quality of life after esophageal cancer surgery. *Qual Life Res* 2014; 23(4):1155-76.
7. Schandl A, Lagergren J, Johar A, et al. Health-related quality of life 10 years after oesophageal cancer surgery. *Eur J Cancer* 2016; 69:43-50.
8. Derogar M, Lagergren P. Health-related quality of life among 5-year survivors of esophageal cancer surgery: a prospective population-based study. *J Clin Oncol* 2012; 30(4):413-8.
9. Derogar M, Orsini N, Sadr-Azodi O, et al. Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery. *J Clin Oncol* 2012; 30(14):1615-9.
10. Rutegard M, Lagergren J, Rouvelas I, et al. Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. *Br J Surg* 2008; 95(5):592-601.
11. Scarpa M, Saadeh LM, Fasolo A, et al. Health-related quality of life in patients with oesophageal cancer: analysis at different steps of the treatment pathway. *J Gastrointest Surg* 2013; 17(3):421-33.
12. van der Schaaf M, Lagergren J, Lagergren P. Persisting symptoms after intrathoracic anastomotic leak following oesophagectomy for cancer. *Br J Surg* 2012; 99(1):95-9.
13. Rutegard M, Lagergren P, Rouvelas I, et al. Surgical complications and long-term survival after esophagectomy for cancer in a nationwide Swedish cohort study. *Eur J Surg Oncol* 2012; 38(7):555-61.
14. Djarv T, Lagergren P. Six-month postoperative quality of life predicts long-term survival after oesophageal cancer surgery. *Eur J Cancer* 2011; 47(4):530-5.
15. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85(5):365-76.
16. Blazeby JM, Conroy T, Hammerlid E, et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *Eur J Cancer* 2003; 39(10):1384-94.

17. Derogar M, van der Schaaf M, Lagergren P. Reference values for the EORTC QLQ-C30 quality of life questionnaire in a random sample of the Swedish population. *Acta Oncol* 2012; 51(1):10-6.
18. Djarv T, Wikman A, Johar A, et al. Poor health-related quality of life in the Swedish general population: the association with disease and lifestyle factors. *Scand J Public Health* 2013; 41(7):744-53.
19. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011; 29(1):89-96.
20. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer* 2012; 48(11):1713-21.
21. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996; 5(6):555-67.
22. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; 16(1):139-44.
23. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* 1999; 48(11):1507-15.
24. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ* 2012; 344:e70.
25. Gerritsen JK, Vincent AJ. Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 2016; 50(13):796-803.
26. Collado-Hidalgo A, Bower JE, Ganz PA, et al. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin Cancer Res* 2006; 12(9):2759-66.
27. Guinan EM, Doyle SL, O'Neill L, et al. Effects of a multimodal rehabilitation programme on inflammation and oxidative stress in oesophageal cancer survivors: the ReStOre feasibility study. *Support Care Cancer* 2017; 25(3):749-756.
28. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 2004; 292(18):2237-42.
29. Tan ZS, Beiser AS, Vasan RS, et al. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. *Neurology* 2007; 68(22):1902-8.
30. Kanekiyo S, Takeda S, Tsutsui M, et al. Low invasiveness of thoracoscopic esophagectomy in the prone position for esophageal cancer: a propensity score-matched comparison of operative approaches between thoracoscopic and open esophagectomy. *Surg Endosc* 2017.
31. Elshiekh MA, Lo TT, Shipolini AR, et al. Does muscle-sparing thoracotomy as opposed to posterolateral thoracotomy result in better recovery? *Interact Cardiovasc Thorac Surg* 2013; 16(1):60-7.
32. Shea RA, Brooks JA, Dayhoff NE, et al. Pain intensity and postoperative pulmonary complications among the elderly after abdominal surgery. *Heart Lung* 2002; 31(6):440-9.
33. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; 250(2):187-96.

34. Schmidt HM, Gisbertz SS, Moons J, et al. Defining Benchmarks for Transthoracic Esophagectomy: A Multicenter Analysis of Total Minimally Invasive Esophagectomy in Low Risk Patients. *Ann Surg* 2017; 266(5):814-821.
35. Kauppila JH, Mattsson F, Brusselaers N, et al. Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study. *BMJ Open* 2018; 8(5):e021495.
36. Kauppila JH, Xie S, Johar A, et al. Meta-analysis of health-related quality of life after minimally invasive versus open oesophagectomy for oesophageal cancer. *Br J Surg* 2017; 104(9):1131-1140.
37. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012; 379(9829):1887-92.

Table 1. Demographics and clinical characteristics of the 616 patients in the total cohort, and of the 92 patients surviving 10 years after esophageal cancer surgery with or without major postoperative complications.

	Total cohort Number = 616		Responders at 10 years Number = 92	
	No complications Number (%)	Complications Number (%)	No complications Number (%)	Complications Number (%)
<b>Total number</b>	317 (51)	299 (49)	55 (60)	37 (40)
<b>Age, median [IQR]</b>	67 [60 - 73]	68 [60 - 74]	73 [68 - 80]	76 [69 - 81]
<b>Sex</b>				
Male	259 (82)	238 (80)	40 (73)	33 (89)
Female	58 (18)	61 (20)	15 (27)	10 (11)
<b>Histology</b>				
Adenocarcinoma	248 (78)	218 (73)	43 (78)	29 (78)
Squamous cell	68 (21)	81 (27)	12 (22)	8 (22)
Missing	1 (0)	0 (0)		
<b>Tumor stage</b>				
I-II	154 (49)	138 (46)	46 (84)	32 (86)
III-IV	159 (51)	156 (52)	9 (16)	5 (14)
Missing	4 (1)	5 (2)	0 (0)	0 (0)
<b>Charlson comorbidity score</b>				
0	38 (12)	37 (12)	6 (11)	5 (14)
1	150 (47)	107 (36)	30 (55)	11 (30)
≥2	129 (41)	155 (52)	19 (35)	21 (57)
<b>Annual surgeon volume</b>				
0-6	150 (47)	115 (38)	23 (42)	16 (43)
≥7	167 (53)	184 (62)	32 (58)	21 (57)

IQR = interquartile range.

Table 2. Postoperative complications occurring within 30 days of esophageal cancer surgery in the 616 patients in the cohort, and in the 92 patients responding to the 10 year follow-up questionnaires.

	Total cohort Number (%)	Responders at 10 year Number (%)
<b>Complications</b>		
No	317 (51)	55 (60)
Yes	299 (49)	37 (40)
<b>Type of complication*</b>		
Major bleeding	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)
Esophagotracheal 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)
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 (0)
Atrial fibrillation	98 (16)	9 (10)
Stroke	5 (1)	1 (1)
Respiratory failure	101 (16)	13 (14)
Pulmonary edema	9 (1)	1 (1)

\*Each patient could have more than one type of complication

**Table 3.** Adjusted relative health-related quality of life (HRQOL) scores and mean score difference (MD) with 95% confidence intervals (CI) from the EORTC QLQ-C30 questionnaire in patients with and without predefined complications after esophageal cancer surgery at different time points from 6 months to 10 years. Values in bold are both clinically relevant and statistically significant.

	Complications at 6 months Number = 402		Complications at 3 years Number = 178		Complications at 5 years Number =141		Complications at 10 years Number = 92	
	No n = 220 (55%)	Yes n = 182 (45%)	No n = 97 (54%)	Yes n= 81 (46%)	No n = 79 (56%)	Yes n = 62 (44%)	No n = 55 (60%)	Yes n = 37 (40%)
	Mean score (95% CI)	Yes vs. no MD (95% CI)	Mean score (95% CI)	Yes vs. no MD (95% CI)	Mean score (95% CI)	Yes vs. no MD (95% CI)	Mean score (95% CI)	Yes vs. no MD (95% CI)
Global HRQOL	64 (60 to 67)	<b>-11 (-15 to -6)</b>	70 (65 to 75)	<b>-15 (-22 to -7)</b>	70 (65 to 75)	<b>-15 (-24 to -7)</b>	68 (61 to 74)	-8 (-17 to 1)
Physical function	79 (75 to 82)	-10 (-13 to -5)	82 (77 to 87)	-10 (-16 to -3)	82 (78 to 87)	-9 (-16 to -1)	84 (78 to 89)	<b>-15 (-24 to -7)</b>
Role function	70 (65 to 75)	-16 (-22 to -9)	75 (68 to 82)	-16 (-26 to -6)	74 (67 to 82)	-14 (-26 to -2)	76 (67 to 85)	-17 (-31 to -4)
Emotional function	75 (71 to 78)	<b>-10 (-19 to -2)</b>	77 (72 to 83)	-7 (-14 to 0)	80 (74 to 85)	-10 (-19 to -2)*	80 (73 to 86)	-7 (-17 to 2)
Cognitive function	82 (79 to 85)	-3 (-7 to 1)	84 (79 to 88)	-5 (-12 to 2)	84 (79 to 89)	-5 (-13 to 3)	81 (75 to 87)	-9 (-18 to 0)*
Social function	74 (70 to 78)	-6 (-12 to -1)	75 (69 to 81)	-4 (-13 to 5)	76 (69 to 83)	-6 (-16 to 4)	81 (73 to 88)	-10 (-21 to 2)
Fatigue	40 (36 to 43)	8 (3 to 14)	33 (27 to 38)	<b>13 (5 to 22)</b>	33 (26 to 39)	11 (1 to 21)	31 (24 to 39)	<b>16 (5 to 26)</b>
Nausea / vomiting	14 (11 to 18)	<b>10 (6 to 15)</b>	11 (6 to 17)	<b>10 (2 to 17)</b>	12 (6 to 18)	<b>9 (1 to 18)</b>	15 (9 to 22)	8 (-1 to 18)
Pain	25 (21 to 29)	5 (0 to 10)	20 (14 to 27)	8 (-1 to 16)	25 (18 to 31)	5 (-5 to 15)	18 (10 to 25)	<b>18 (7 to 30)</b>
Dyspnea	28 (23 to 32)	<b>12 (6 to 18)</b>	20 (13 to 27)	<b>19 (9 to 28)</b>	23 (15 to 30)	<b>16 (4 to 27)</b>	28 (20 to 37)	<b>15 (2 to 27)</b>
Insomnia	20 (16 to 24)	5 (0 to 11)	18 (11 to 24)	4 (-5 to 13)	17 (10 to 25)	4 (-7 to 14)	21 (13 to 30)	<b>20 (8 to 32)</b>
Appetite	33 (28 to 38)	12 (5 to 18)	26 (18 to 33)	14 (3 to 25)*	23 (15 to 32)	12 (-1 to 24)	20 (10 to 30)	12 (-2 to 26)
Constipation	9 (5 to 12)	5 (1 to 9)	4 (-1 to 9)	2 (-5 to 9)	5 (0 to 10)	2 (-6 to 10)	8 (2 to 14)	3 (-6 to 12)
Diarrhea	32 (27 to 37)	-1 (-8 to 5)	33 (26 to 40)	2 (-8 to 12)	34 (27 to 42)	0 (-12 to 12)	21 (12 to 30)	<b>19 (5 to 32)</b>
Financial	12 (8 to 16)	6 (1 to 11)	11 (6 to 17)	5 (-3 to 13)	11 (4 to 17)	6 (-3 to 15)	9 (2 to 16)	<b>15 (5 to 26)</b>

\*Rounded value, not clinically relevant; vs. = versus; n = number

**Table 4.** Adjusted relative health-related quality of life (HRQOL) scores and mean score difference (MD) with 95% confidence intervals (CI) from the EORTC QLQ-OES18 questionnaire in patients with and without predefined complications after esophageal cancer surgery at different time points from 6 months to 10 years. Values in bold are both clinically relevant and statistically significant.

	Complications at 6 months Number = 402		Complications at 3 years Number = 178		Complications at 5 years Number = 141		Complications at 10 years Number = 92	
	No n = 220 (55%)	Yes n = 182 (45%)	No n = 97 (54%)	Yes n = 81 (46%)	No n = 79 (56%)	Yes n = 62 (44%)	No n = 55 (60%)	Yes n = 37 (40%)
	Mean score (95% CI)	Yes vs. no MD (95% CI)	Mean score (95% CI)	Yes vs. no MD (95% CI)	Mean score (95% CI)	Yes vs. no MD (95% CI)	Mean score (95% CI)	Yes vs. no MD (95% CI)
Eating restrictions	33 (29 to 37)	7 (2 to 11)	28 (23 to 34)	8 (0 to 16)	25 (19 to 31)	9 (0 to 18)	24 (17 to 31)	<b>14 (3 to 24)</b>
Reflux	24 (20 to 28)	3 (-2 to 9)	22 (15 to 28)	1 (-8 to 10)	22 (15 to 29)	2 (-9 to 13)	38 (30 to 46)	1 (-11 to 12)
Esophageal pain	27 (23 to 30)	3 (-1 to 8)	25 (20 to 30)	1 (-6 to 9)	26 (20 to 32)	-2 (-10 to 7)	16 (9 to 22)	<b>13 (4 to 23)</b>
Dysphagia	21 (18 to 25)	5 (0 to 9)	16 (10 to 21)	6 (-2 to 14)	15 (8 to 21)	3 (-6 to 13)	20 (13 to 26)	-2 (-12 to 8)
Cough	22 (17 to 26)	<b>12 (6 to 18)</b>	21 (14 to 27)	8 (-2 to 18)	21 (13 to 28)	3 (-8 to 15)	26 (17 to 34)	3 (-10 to 16)
Dry mouth	29 (24 to 33)	2 (-4 to 8)	23 (17 to 30)	2 (-8 to 12)	22 (14 to 29)	0 (-12 to 11)	25 (16 to 33)	5 (-8 to 17)
Taste	19 (14 to 23)	<b>11 (6 to 18)</b>	14 (7 to 20)	<b>12 (2 to 22)</b>	15 (7 to 22)	7 (-4 to 18)	12 (4 to 21)	5 (-8 to 17)
Choking	17 (14 to 21)	9 (4 to 14)	14 (9 to 20)	<b>12 (4 to 20)</b>	12 (6 to 18)	<b>13 (4 to 23)</b>	14 (7 to 21)	<b>16 (5 to 27)</b>
Speaking	13 (10 to 17)	6 (1 to 11)	11 (5 to 16)	9 (2 to 17)	9 (3 to 15)	7 (-2 to 16)	10 (3 to 16)	8 (-2 to 17)
Swallowing saliva	12 (8 to 16)	5 (0 to 10)	11 (5 to 16)	5 (-3 to 14)	11 (4 to 17)	2 (-8 to 12)	10 (3 to 17)	<b>12 (1 to 23)</b>

vs. = versus; n = number