


# Impact of co-morbidities on health-related quality of life 10 years after surgical treatment of oesophageal cancer

F. Klevebro<sup>1</sup> , A. Johar<sup>1</sup> and P. Lagergren<sup>1,2</sup> 

<sup>1</sup>Surgical Care Science, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, and <sup>2</sup>Department of Surgery and Cancer, Imperial College London, London, UK

Correspondence to: Dr F. Klevebro, Surgical Care Science, Department of Molecular Medicine and Surgery, Karolinska Institutet, Norra Stationsgatan 67, 2nd Floor, 17176 Stockholm, Sweden (e-mail: fredrik.klevebro@ki.se)

**Background:** Oesophagectomy for cancer is associated with long-term decreased health-related quality of life (HRQoL). The aim of this study was to evaluate the effect of co-morbidities on HRQoL among survivors of oesophageal or gastro-oesophageal junctional cancers after 10 years or more.

**Methods:** The study included a prospectively collected, population-based cohort, comprising all patients who had surgery for oesophageal or gastro-oesophageal junctional cancer in Sweden in 2001–2005 with follow-up until 31 December 2016. All data regarding patient and tumour characteristics, treatment details and HRQoL were collected using a prospectively created database. Multivariable ANCOVA regression models, adjusting for age, sex, tumour histology, stage and surgical technique, were used to calculate adjusted mean scores with 95 per cent confidence intervals for all HRQoL outcomes.

**Results:** A total of 92 survivors (88.5 per cent) responded to the questionnaires. Patients were stratified in two groups according to whether they reported a low or high impact of co-morbidities on general health. Patients in the high-impact group had clinically significantly decreased HRQoL and an increased level of symptoms, but differences between these two groups were not statistically significant.

**Conclusion:** Co-morbidities with high impact on general health still contribute to impaired HRQoL 10 years after oesophagectomy for cancer.

#### Funding information

Cancerfonden  
Cancerföreningen i Stockholm

Paper accepted 4 May 2020

Published online 29 May 2020 in Wiley Online Library (www.bjsopen.com). DOI: 10.1002/bjs.5.50303

## Introduction

The morbidity of oesophagectomy is among the highest of all surgical procedures<sup>1</sup> and health-related quality of life (HRQoL) is affected negatively for up to 10 years after treatment<sup>2,3</sup>. Treatment of oesophageal cancer has improved in recent years, with the introduction of enhanced recovery programmes and minimally invasive surgical techniques<sup>4,5</sup>, but patient characteristics still play an important role. Co-morbidity at surgery is a known risk factor for poor HRQoL, and acquired co-morbidities might affect HRQoL in the long term<sup>6</sup>. It is unclear, however, how co-morbidities are related to long-term HRQoL after oesophagectomy. The present study aimed to determine whether a high impact of co-morbidities on subjective general health was associated with decreased HRQoL in patients who had survived 10 years after treatment for

oesophageal or gastro-oesophageal junctional cancer. This might guide tailored follow-up and influence survivorship.

## Methods

The design of this Swedish nationwide cohort study has been presented in detail elsewhere<sup>7–10</sup>. The study cohort included 90 per cent of all patients who underwent oesophagectomy for oesophageal or gastro-oesophageal junctional cancer in Sweden between 1 April 2001 and 31 December 2005, with follow-up until 31 December 2016. The majority of patients had oesophagectomy alone; 5 per cent received neoadjuvant therapy. Clinical data were collected in a prospectively developed database from medical records based on a predefined study protocol, and included patient and tumour characteristics as well as treatment details.

## Exposure

The study cohort was stratified by the reported effect of co-morbidity on general health in a follow-up questionnaire 10 years after treatment. Patients were asked if a physician had diagnosed any co-morbidities after their oesophageal cancer diagnosis and, if so, to list them and grade the impact of each co-morbidity on their general health. Possible responses were: 1, not at all; 2, a little; 3, quite a bit; and 4, very much. Patients were stratified in two groups according to the responses: patients without co-morbidities and those responding 1 or 2 were classified as the low-impact group; patients with responses 3 or 4 were classified as the high-impact group.

## Outcomes and clinical data

The outcomes were HRQoL and symptoms reported on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-OES18 questionnaires. The response alternatives to each question in both questionnaires were: 1, not at all; 2, a little; 3, quite a bit; and 4, very much. The only exception was for the global HRQoL scale; this has two items – self-reported health and quality of life – with ratings ranging from 1 (very poor) to 7 (excellent). The validated core questionnaire (EORTC QLQ-C30) was used to measure aspects of HRQoL and symptoms that are applicable to patients with cancer in general, whereas the validated oesophageal cancer-specific module (EORTC QLQ-OES18) measured common symptoms among patients with oesophageal cancer. HRQoL was assessed 6 months, 3, 5 and 10 years after surgery. For the purpose of this study, only the 10-year follow-up questionnaires were used to compare the two groups. All questionnaires were self-administered, were delivered by mail and up to three reminders were sent if required. Collection of HRQoL data was done anonymously; patients sent their answers to a central administration and not to the treating department. The Regional Ethical Review Board in Stockholm, Sweden, approved that the study met the requirements for protection of human subjects.

## Statistical analysis

All questionnaire responses were transformed linearly to scores ranging from 0 to 100, according to the scoring procedure in the EORTC manual<sup>11</sup>. Concerning HRQoL, higher scores represent better HRQoL, whereas higher scores in symptom scales represent more symptoms. Missing data were managed as recommended in the EORTC scoring manual<sup>11</sup>. ANCOVA regression

**Table 1 Characteristics of patients included in the health-related quality-of-life analysis 10 years after treatment with curative intent for oesophageal or gastro-oesophageal junctional cancer**

	Low impact of co-morbidity (n = 60)	High impact of co-morbidity (n = 32)
<b>Age (years)*</b>	73 (41–89)	73 (58–84)
<b>Sex ratio (F : M)</b>	14 : 46	5 : 27
<b>Histological tumour type</b>		
Squamous cell carcinoma	12 (20)	8 (25)
Adenocarcinoma	48 (80)	24 (75)
<b>Tumour stage</b>		
0–I	32 (53)	17 (53)
II	17 (28)	12 (38)
III	10 (17)	3 (9)
IV	1 (2)	0 (0)
<b>Surgical approach</b>		
Transthoracic oesophagectomy	51 (85)	25 (78)
Transhiatal oesophagectomy	8 (13)	6 (19)
Three-stage oesophagectomy	1 (2)	1 (3)

Values in parentheses are percentages unless indicated otherwise; \*values are mean (range).

**Table 2 Co-morbidities listed by patients 10 years after treatment with curative intent for oesophageal or gastro-oesophageal junctional cancer**

	Low impact of co-morbidity (n = 60)	High impact of co-morbidity (n = 32)
Gastrointestinal	11 (18)	8 (25)
Cardiovascular	9 (15)	7 (22)
Pulmonary	3 (5)	6 (19)
Malignancy	9 (15)	7 (22)
Diabetes	0 (0)	1 (3)
Orthopaedic	1 (2)	6 (19)
Urological	7 (12)	7 (22)
Neurological	0 (0)	1 (3)
Autoimmune	0 (0)	2 (6)
Other	7 (12)	6 (19)
Total no. of co-morbidities*	47	51

\*Each patient could report more than one co-morbidity.

models were used to calculate adjusted mean scores with 95 per cent confidence intervals for all HRQoL outcomes. A mean score difference of 10 or more was considered clinically relevant, and was further tested for statistical significance<sup>12–14</sup>. The following potential confounders were included in the adjusted models: age (continuous), sex, histological tumour type (squamous cell carcinoma or adenocarcinoma), tumour stage (TNM 0–I, II, III or IV)

**Table 3 Health-related quality of life 10 years after oesophageal cancer surgery assessed using EORTC questionnaires, according to impact of co-morbidity**

	Adjusted mean score*	
	Low impact of co-morbidity (n = 60)	High impact of co-morbidity (n = 32)
<b>EORTC QLQ-C30</b>		
Global health status	69.5 (52.9, 86.1)	63.2 (45.5, 81.0)
Physical functioning	81.7 (66.5, 96.8)	78.8 (62.7, 94.9)
Role functioning	75.6 (51.6, 99.5)	65.7 (39.8, 91.5)†
Emotional functioning	86.9 (70.8, 102.9)	81.8 (64.7, 100.0)
Cognitive functioning	91.6 (75.4, 107.7)	90.8 (73.5, 108.0)
Social functioning	93.0 (75.6, 110.4)	78.8 (60.2, 97.4)†
Fatigue	25.3 (4.9, 45.7)	26.1 (4.3, 47.9)
Nausea and vomiting	13.5 (-5.7, 15.4)	17.4 (-3.1, 37.9)
Pain	10.5 (-8.6, 29.5)	21.8 (1.4, 42.2)†
Dyspnoea	17.5 (-5.9, 41.0)	22.2 (-2.9, 47.3)
Insomnia	29.2 (4.8, 53.5)	25.0 (-1.1, 51.0)
Appetite loss	12.3 (-14.9, 39.5)	22.4 (-6.7, 51.6)†
Constipation	5.7 (-12.4, 23.7)	9.9 (-9.4, 29.1)
Diarrhoea	25.3 (3.4, 47.1)	37.7 (14.5, 60.9)†
Financial difficulties	2.4 (-15.1, 19.8)	14.4 (-4.3, 33.2)†
<b>EORTC QLQ-OES18</b>		
Dysphagia	30.0 (10.4, 49.6)	21.4 (0.3, 42.6)
Eating problems	28.2 (9.8, 46.6)	38.9 (19.2, 58.6)†
Reflux	34.7 (13.4, 56.1)	34.5 (11.7, 57.4)
Pain	13.9 (-2.5, 30.2)	21.9 (4.4, 39.4)
Trouble swallowing saliva	12.0 (-2.8, 26.8)	3.6 (-13.5, 20.7)
Choked when swallowing	11.5 (-8.0, 31.1)	16.6 (-4.5, 37.7)
Dry mouth	7.8 (-12.2, 27.8)	22.3 (0.9, 43.7)†
Trouble with taste	12.8 (-6.4, 31.9)	16.6 (-3.8, 37.0)
Trouble with coughing	10.2 (-12.9, 33.4)	11.4 (-13.3, 36.2)
Trouble with talking	18.6 (2.5, 34.7)	23.8 (6.6, 41.0)

Values in parentheses are 95 per cent confidence intervals. \*Adjusted for age, sex, histological tumour type, tumour stage and surgical technique. Model for trouble swallowing saliva was adjusted only for age and stage; other confounders were removed owing to issues with model estimation. †Clinically significant differences. EORTC, European Organisation for Research and Treatment of Cancer.

and surgical technique (transthoracic oesophagectomy, transhiatal oesophagectomy, gastrectomy, or gastrectomy and oesophageal resection combined). All analyses were conducted by an experienced biostatistician according to a predefined study protocol. The statistical software used was SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA).

## Results

Of 616 patients included in the original study, 104 (16.9 per cent) were alive, of whom 92 (88.5 per cent) responded

to HRQoL questionnaires 10 years after treatment. The impact of co-morbidities on general health was reported as none or low by 60 patients (65 per cent), whereas 32 patients (35 per cent) reported a high impact. Patient characteristics were similar in the low- and high-impact groups (Table 1).

The 60 patients in the low-impact group reported a total of 47 co-morbidities, and the 32 patients in the high-impact group reported 51 (Table 2). Gastrointestinal co-morbidities were the most common in both groups.

Patients who experienced a high impact of co-morbidity on health reported clinically relevant worse scores for role and social functioning, as well as financial difficulties, but the differences were not statistically significant (Table 3). Similarly, patients in the high-impact group reported more pain, appetite loss and diarrhoea considered clinically relevant, but this was not statistically significant. With regard to oesophageal-specific symptoms, clinically more problems were reported for eating issues and dry mouth in the high-impact group than in the low-impact group, but again without statistical significance (Table 3). Insomnia and fatigue were reported at relatively high levels in both groups.

## Discussion

This study showed that co-morbidity affecting patients' reported general health to a high level had a negative impact on role and social functioning, and increased financial difficulties, pain, appetite loss and diarrhoea 10 years after oesophageal cancer surgery. Although differences were not statistically significant, they reached a level of clinical importance. These results provide some explanation as to why some patients still report poor HRQoL 10 years after cancer treatment.

Strengths of the study include the population-based prospective design, and long follow-up. HRQoL was measured using validated questionnaires, which reduces the risk of information bias and increases the comparability of the results with those of other research studies. All clinical data were collected according to a predefined protocol, and medical records were scrutinized by researchers not involved in the care of the patients. The variables included in the multivariable regression model were pre-specified. Limitations of the study include the small sample size, which reflects the poor long-term survival of patients with oesophageal cancer. The response rate among surviving patients was very high, which reduces the risk of selection bias.

In a previous study<sup>3</sup> based on the same cohort, HRQoL among patients 10 years after treatment was reported

as decreased in all measured variables compared with a matched reference population; the results also showed a decline in 23 of the 25 variables measured between 5 and 10 years after operation. The reasons behind this deterioration in surviving patients are likely to be multifactorial. Other studies<sup>15–17</sup> have shown that complications of treatment as well as eating problems have a significant impact on HRQoL 10 years after treatment. In an analysis of HRQoL in the present cohort 5 years after treatment<sup>6</sup>, patients with increased co-morbidities showed a deterioration in HRQoL compared with those who had no or stable co-morbidities, indicating that co-morbidities have an important impact on long-term HRQoL.

Co-morbidities with a high reported impact on general health can be associated with symptoms and decreased HRQoL for more than 10 years after oesophagectomy for cancer. This information may be useful in tailoring the follow-up and influence survivorship.

### Acknowledgements

The Stockholm Cancer Society and the Swedish Cancer Society provided funding. The sponsors had no involvement in the study.

*Disclosure:* The authors declare no conflict of interest.

### References

- Schieman C, Wigle DA, Deschamps C, Nichols FC III, Cassivi SD, Shen KR *et al.* Patterns of operative mortality following esophagectomy. *Dis Esophagus* 2012; **25**: 645–651.
- Scarpa M, Valente S, Alfieri R, Cagol M, Diamantis G, Ancona E *et al.* Systematic review of health-related quality of life after esophagectomy for esophageal cancer. *World J Gastroenterol* 2011; **17**: 4660–4674.
- Schandl A, Lagergren J, Johar A, Lagergren P. Health-related quality of life 10 years after oesophageal cancer surgery. *Eur J Cancer* 2016; **69**: 43–50.
- Wang L, Zhu C, Ma X, Shen K, Li H, Hu Y *et al.* Impact of enhanced recovery program on patients with esophageal cancer in comparison with traditional care. *Support Care Cancer* 2017; **25**: 381–389.
- Gemmill EH, Humes DJ, Catton JA. Systematic review of enhanced recovery after gastro-oesophageal cancer surgery. *Ann R Coll Surg Engl* 2015; **97**: 173–179.
- Backemar L, Wikman A, Djarv T, Johar A, Lagergren P. Co-morbidity after oesophageal cancer surgery and recovery of health-related quality of life. *Br J Surg* 2016; **103**: 1665–1675.
- 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**: 413–418.
- Viklund P, Lindblad M, Lu M, Ye W, Johansson J, Lagergren J. Risk factors for complications after esophageal cancer resection: a prospective population-based study in Sweden. *Ann Surg* 2006; **243**: 204–211.
- Wikman A, Ljung R, Johar A, Hellstadius Y, Lagergren J, Lagergren P. Psychiatric morbidity and survival after surgery for esophageal cancer: a population-based cohort study. *J Clin Oncol* 2015; **33**: 448–454.
- Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. *J Clin Oncol* 2009; **27**: 1963–1968.
- Fayers PAN, Bjordal K, Groenvold M, Curran D, Bottomley A. *The EORTC QLQ-C30 Scoring Manual*. European Organisation for Research and Treatment of Cancer: Brussels, 2001.
- Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**: 139–144.
- Blazeby JM, Alderson D, Winstone K, Steyn R, Hammerlid E, Arraras J *et al.* Development of an EORTC questionnaire module to be used in quality of life assessment for patients with oesophageal cancer. The EORTC Quality of Life Study Group. *Eur J Cancer* 1996; **32A**: 1912–1917.
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *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**: 365–376.
- Kauppila JH, Johar A, Lagergren P. Medical and surgical complications and health-related quality of life after esophageal cancer surgery. *Ann Surg* 2018; **271**: 502–508.
- Kauppila JH, Johar A, Lagergren P. Postoperative complications and health-related quality of life 10 years after esophageal cancer surgery. *Ann Surg* 2018; **271**: 311–316.
- Anandavadevelan P, Wikman A, Johar A, Lagergren P. Impact of weight loss and eating difficulties on health-related quality of life up to 10 years after oesophagectomy for cancer. *Br J Surg* 2017; **105**: 410–418.