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Title page

Quality of life after minimally invasive esophagectomy: a cross-sectional study

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Short title: Quality of life after esophagectomy

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Abstract

Introduction: Surgery remains essential in the curative treatment of esophageal cancer (EC), but it is known for its high morbidity and impaired health-related QoL. Minimally invasive esophagectomy (MIE) was introduced to reduce surgical trauma and improve QoL.

Methods: This cross-sectional study aimed to evaluate long-term HRQoL after MIE in comparison to the general population. HRQoL assessment was based on three questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) Core 30 (QLQ-C30, version 3), the EORTC QLQ Oesophago Gastric 25 (QLQ-OG25), and the Supportive Care Needs Survey-Short Form34 (SCNS-SF34). Results were compared to a healthy reference population.

Results: One hundred and forty eligible MIE patients were identified, of whom met the inclusion criteria, and 49 completed all questionnaires. Patients reported a significantly better mean score on the global health status and QoL than the healthy reference population (71.5 ± 15.1 versus 66.1 ± 21.7; *p*=0.016). However, patients scored significantly worse about functioning (physical, role and social) (*p*<0.05), fatigue (*p*=0.021), eating, dysphagia, pain and discomfort, reflux, appetite loss, weight loss, coughing, and taste (*p*< 0.001).

Discussion/Conclusion: EC survivors can reach a high global health status and QoL at least one year after MIE, despite long-term functional, nutritional and gastrointestinal complaints.

Patients provided written informed consent, and the study protocol was approved by the ethics committee of Ghent University hospital (identifier: ID B670201940737).

Main text

Introduction

Esophageal cancer (EC) is commonly treated multimodal with surgery, radiotherapy and/or chemotherapy according to the stage and location of the tumour. Despite extensive changes in therapeutic modalities, surgery remains essential in the curative treatment for EC, but it is known for its high morbidity and mortality [1, 2]. Literature reports short term morbidity rates up to 59% and 30 and 90-day mortality rates of 6% and 13%, respectively [3, 4]. Long-term quality of life (QoL) studies associate esophageal surgery with impaired QoL due to life-long complaints of pain, cough, shortness of breath, weight loss, reflux, dysphagia, diarrhoea, nausea, and eating problems [5, 6].

Over the past two decades, minimally invasive esophagectomy (MIE) and robotically-assisted MIE (RAMIE) were introduced to reduce surgical trauma and improve QoL [7, 8]. MIE results in a reduction of blood loss, pulmonary complications, and length of stay [9]. Most studies focus on the clinical and oncological outcomes; however, few studies focus on patient-reported outcomes. HRQoL is an essential outcome measure for oncological treatment [10]. HRQoL is a multidimensional concept measuring the effect on physical, emotional, cognitive, and social wellbeing, and on role functioning, sexuality and spirituality [11]. MIE is associated with faster recovery and a better short term HRQoL compared to open surgery [12]. However, literature on long-term HRQoL after MIE compared to a healthy reference population is scarce. This study aimed to evaluate long-term HRQoL after MIE and the need for long-term supportive care in comparison to a reference population.

Materials and Methods

Design

A cross-sectional study was conducted to explore HRQoL and supportive needs in patients after MIE. Patients consented to the study and the study was approved by the Ghent University hospital Ethics committee (identifier: ID B670201940737).

Setting and participants

All EC patients treated with MIE between October 2015 and May 2019 at the department of GI Surgery of Ghent University Hospital and who met the inclusion criteria were included in the study. All Dutch-speaking patients who were competent to consent and who had surgery at least one year before the study and had no known recurrence were eligible. Deceased patients and patients with cognitive impairment were excluded.

Data collection

Questionnaires: HRQoL was assessed using three questionnaires: the EORTC QoL Questionnaire Core 30 (QLQ-C30, version 3), the EORTC QoL Questionnaire - Oesophago-Gastric (QLQ-OG25, specific module), and the Supportive Care Needs Survey-Short Form 34 (SCNS-SF34). Permission was obtained for all questionnaires.

The EORTC QLQ-C30 questionnaire is a validated and reliable measurement tool originally developed in English but translated into more than 100 languages. The EORTC QLQ-C30 consists of 30 items with five functional scales (physical, role, cognitive, emotional and social), eight symptom scales (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, lack of appetite, diarrhoea, constipation and financial difficulties) and a scale for determining global health status and QoL [13, 14, 15]. The EORTC QLQ-OG25 was specifically developed for patients with cancer of the oesophagus, stomach and gastroesophageal junction. The questionnaire consists of 25 items subdivided into 6 symptom scales (dysphagia, odynophagia, reflux symptoms, eating disorders, pain and discomfort and anxiety) [16]. Both questionnaires score items on a four-point Likert scale ('not at all', 'a little', 'rather', 'very much'), except the last two items in the EORTC QLQ-C30 (global health status and quality of life) which have seven-point answer options (from very poor to excellent)[15].

The SCNS-SF34 is a widely used questionnaire to determine the need for supportive care in patients diagnosed with cancer[17]. It was validated and translated into Dutch[18]. The questionnaire consists of 34 items divided into five domains: physical and daily life (5 items), psychological (10 items), sexuality (3 items), patient care and support (5 items), and health system and information (11 items). Each item is scored on a five-point Likert scale that is divided into two levels, 'no need' and 'need'. The level 'no need' is further subdivided into 'not applicable' and 'satisfied'. The 'need' level has three categories (low, average and high need) [18, 19].

Demographic and clinical data: Demographic data, including gender, age, marital status, employment status and highest obtained educational degree, of the patients, were collected. Clinical data on co-morbidities, post-operative complications, American Society of Anaesthesiologists (ASA) score, tumour characteristics and data on neoadjuvant therapy were obtained retrospectively from the hospital records. Postoperative complications were recorded until 30 days postoperatively. Tumours were staged according to the TNM classification.

Reference population: The data obtained from the EORTC QLQ-C30 of EC patients undergoing a MIE were compared with the published reference values of a healthy European population (n = 11 343; age ranging from 18 to 99 years; 50.4% males and 49.6% females)[20]. The EORTC QLQ-OG25 data were compared with a published healthy reference group of 4910 people (age ranging from 40 to 79 years; 69.9% men and 30.1% women)[21]. No reference population was available for the SCNS-SF34.

Data analysis

Derived scores from the EORTC QLQ-30 and EORTC QLQ OG25 were linearly transformed into scores varying from 0-100, according to the EORTC scoring manual. A high score on the functional scales, global health status and QOL represents a high QOL and a better level of functioning, while a high score on symptom scales and individual items suggests a higher level of complaints [15]. For the SCNS-SF34 a total score per domain was calculated and transformed into a score from 0 to 100. The higher the score, the higher the need for supportive care [19]. Missing data were addressed according to the recommendations of the EORTC and Supportive Care Needs Survey [15, 19].

Using descriptive statistics, the demographic data, clinical data, and the results of the questionnaires were tabulated after exclusion of extreme values. Continuous variables were presented as mean and standard deviation (SD) while the categorical variables were summarized with frequencies and percentages. For non-normally-distributed continuous variables, the median and interquartile ranges (IQR) were calculated. To compare the average scores of the EORTC QLQ-C30 and the EORTC QLQ-OG25 with a healthy reference group, the One-Sample T-test was used. If the continuous variables were not normally distributed, a log transformation (using the natural logarithm) was performed. When the transformation did not contribute to a normal distribution of the continuous variable, the One-Sample Wilcoxon Signed Rank test was applied. Eventually, by means of multiple linear regression with a backward selection procedure, predictive factors influencing the long-term HRQoL were identified.

The global health status and QoL of the EORTC QLQ-C30 was entered as the dependent variable and a set of possible determinants as the independent variables. Gender, neoadjuvant therapy, smoking status, ASA-score, diabetes, cardiovascular events, anastomotic leakage and pneumonia were chosen as determinants based on previous studies. Each variable was coded to a dummy variable where 0 (= reference) stands for 'not applicable' and 1 for 'applicable'. In practice, the ASA score mainly illustrated ASA II and III because all patients had been diagnosed with cancer (> I) and none had been classified with ASA IV. Due to a large number of variables about the sample size, we performed a pre-selection first. Using single linear regression analysis, the relationship with the dependent variable was examined for each potential predictive variable. With a p-value below 20%, the variables were included in the basic model and further analysed via the backward selection procedure, variables that contributed the least were gradually removed from the multiple linear regression model (p-value > 0.10) until only those variables remained that made a relevant contribution to the prediction of the dependent variable. All statistical analyses were performed using the IBM SPSS Statistics program, version 26 (IBM Corporation, 2019, Armonk, New York, United States). The significance level was set to a p-value < 0.05.

Results

Participants

One hundred and forty eligible MIE patients were identified from the esophageal surgery database. At the time of analysis 46 patients (33%) had died, and 11 patients (7%) had a known metastatic or local recurrence. One patient (1%) was excluded because of a mental disorder. The remaining 83 patients (59%) were alive and disease-free more than 1y after their surgery, 49 (59%) of whom completed all questionnaires in full. The reasons for not responding to the questionnaires are unclear as the study invitation was sent through post and mail, and no reasons for not responding were asked. The univariate analysis could not identify statistically significant differences in demographics, clinical variables and postoperative complications between questionnaire responders and non-responders, except for a more frequent presence of squamous cell carcinoma in the non-responders group (p=0.004).

The mean time between surgery and study participation was 30 ± 11.4 months. Most patients were male (83.7%), non-smoker (83.7%), married (67.3%), and retired (81.3%). The mean age was 71±9 years. Most patients were diagnosed with stage III EC (53.5%), had a distal (67.6%) adenocarcinoma (89.1%) and received neoadjuvant (radio)chemotherapy (65.3%). All patients had an ASA score of II (50.0%) or III (50%) before surgery, mainly based on a history of cardiovascular events (57.1%), diabetes (14.3%), or renal insufficiency (4.1%). Postoperative complications such as anastomotic leakage (10.2%) and pneumonia (20.4%) were within the normal range according to the literature.

Long-term HRQoL compared to the reference population

The mean and median EORTC QLQ-C30 and EORTC QLQ-OG25 scores are presented in table 1. MIE patients scored significantly lower on the functional scales compared to the reference population (Figure 1). Controversially, they scored global health status and QoL significantly higher compared to the healthy reference population (71.5 ± 15.1 versus 66.1 ± 21.7; p=0.016), even though they experienced more symptoms such as fatigue (p=0.021), pain and discomfort (p<0.001), trouble with taste (p<0.001) and trouble with coughing (p<0.001). Patients after MIE also reported more eating, dysphagia and reflux problems as well as a loss of appetite and weight loss (p < 0.001). However, they experienced less nausea and vomiting, dyspnoea, diarrhoea, odynophagia and dry mouth (p < 0.05) compared to the reference population Figure 2. Hair loss was only reported by a few patients (28.6%), making them not (85.7%) or somewhat upset (14.3%) (Table 1).

Supportive care needs

Psychological supportive care was needed the most (30.08 ± 25.10) followed by the need for health system support and information support (29.59 ± 25.55). EC patients reported uncertainty about the future (29.2%), worries about the people close to them (27.1%) and fear about cancer spreading (27.1%) as the most frequent medium or high needed supportive need areas. Concerning the health system and information needs, urgent information on test results (27.1%) and information on cancer control (29.2%) were reported as moderate or high needs, which were often not adequately addressed. Supportive care about their sexual needs received the lowest score (Table 2).

Predictive factors for HRQoL

Through multiple linear regression with a backward selection procedure, a prediction model was created. The dependent variable was global health status and QoL measured at least one year after MIE with the EORTC QLQ-C30. Due to the small sample size, a pre-selection was made before the backward selection procedure. Only the ASA score was a significant predictor of the overall health status and QoL. The overall health status and QoL was significantly better in patients classified with ASA-score II compared to patients classified with ASA-score III (regression coefficient (b) 11.5; 95% confidence interval (CI) 3.2-19.8; p=0.008). Thus, only one predictive variable was included in the final model. The adjusted R square showed that 13.0% of the variance in overall health status and QoL is explained by the ASA score.

Discussion

Long-term QoL studies associate esophageal surgery with impaired QoL due to life-long digestive complaints. Minimally invasive techniques were introduced to reduce surgical trauma and improve QoL. However, most MIE studies focus on short term clinical and oncological outcome, while very few studies focus on patient-reported outcomes. Moreover, literature on long-term HRQoL and the need for long-term supportive care in comparison to a reference population is lacking.

This cross-sectional study aimed to investigate the long-term HRQoL in MIE patients at least one year after their surgery in comparison to a healthy reference population. Until now it was unclear if EC patients return to a normal HRQoL after MIE. Our study shows that it is possible to experience a high global health status and QoL at least one year after surgery. Surprisingly, EC survivors reported significantly higher scores compared to the healthy reference population, even though most patients experienced more clinical and functional complaints. Previous studies have shown contradicting long-term HRQoL results: some showed a continued decline in HRQoL [22, 23] while others, including the present study, reported a comparable or even a better global health status and QoL in patients without recurrence.[24, 25]. This high score on global health and QoL could be the result of a response shift, meaning an adjustment of the perception of the HRQoL and changes in the meaning of one's self-evaluation. This can be a result of changes in the internal standards (recalibration), personal values (reprioritization) or the meaning of the measured construct (reconceptualization). As a result, patients learn to cope with their new living conditions and therefore their response can change over time [26, 27]. Our study population only included MIE patients which might also explain the high long-term HRQoL scores, as previous research groups reported better long-term HRQoL after MIE compared to open surgery [12, 28].

In accordance with others studies, we found that patients experience lasting clinical, nutritional and gastrointestinal symptoms such as fatigue, lack of appetite, problems with eating, and reflux [22-25, 28]. Anatomical and physiological changes after surgery may cause eating disorders and reflux. However, the high global health status and QoL scores suggest that patients accept the changed eating behaviour over time [24]. EC survivors reported less pain than the reference population, probably due to different reference frames: while cancer survivors only report disease-specific pain, the general population reports various everyday pains [29]. Similar to the work of Däster et al., we found higher emotional and cognitive functioning scores in EC survivors compared to the healthy population. A potential explanation is patient age: 85.7% was ≥ 60 years old in the current study, compared to 40.5% in the general population. It is known that people adjust their health expectations when they get older [20].

In line with the findings of Backemar et al., we also identified a higher ASA score as an important predictor of lower overall health status and long-term QoL [30]. Unlike other studies, we did not find an association between other risk factors such as neoadjuvant treatment and the presence of comorbidities with impaired QoL [23, 28, 30]. This lack of association may be due to the small sample size.

Similar to the findings of Jezerskyte et al., we could not identify postoperative complications as a predictor of impaired HR-QoL more than 1 year after surgery. Their comparison of short and long term HR-QoL after complicated and non-complicated esophagectomies showed an equal temporary decrease in HR-QoL. They concluded that postoperative complications were not associated with decreased short- and long-term HR-QoL. Due to the cross-sectional design, we could not address the evolution of HR-QoL after MIE. However, Jezerskyte and co-workers investigated HR-QoL at baseline and at 3,6,9,12,18, and 24 months after surgery. They found a significant decline in short term HR-QoL after complicated as well as after non-complicated esophagectomy, which recovered to baseline during the following 12 months after surgery [31].

To provide cancer survivors with adequate care tailored to their needs, this study examined their supportive care needs at least one year after a MIE. We found continued unmet care needs, mainly concerning psychological needs, health system and information needs, consistent with results from supportive care need studies in patients with other types of cancer [32]. The lowest level of unmet support needs concerned sexuality, which is consistent with previous studies [32]. However, because of taboo, patients may be ashamed to indicate sexual problems.

The study has a low percentage of missing data (1.4%) and a relatively high response rate (59.0%). Validated questionnaires were used to avoid information bias. By anonymizing the questionnaires, socially desirable responses were avoided, reducing the response bias. To further reduce bias, we interviewed a very coherent patient cohort after identical MIE surgery, in contrast to other publications covering multiple different surgical procedures.

This study carried some methodological limitations. The number of patients included is small, which limits the robustness of the statistical analyses. However, a response rate of 60% has been used as the threshold of acceptability and has face validity as a measure of survey quality. Due to the cross-sectional design, we were unable to detect changes in scores of the HRQoL over time. Also, no data were collected at baseline, therefore the recovery of the HRQoL to a level before the procedure could not be verified. This bias is however limited concerning the long term HR-QoL, as suggested by the work of Jezerskyte et al. They found a significant temporary decline in short term HR-QoL, which restored to baseline levels during the following 12 months after surgery [31]. Our findings complement the above by concluding that EC survivors can reach high global health status and QoL at least one year after MIE in comparison to a healthy reference population despite long-term functional, nutritional and gastrointestinal complaints.

In addition, causality could not be discussed because of the cross-sectional design. The non-probabilistic sampling (consecutive sampling) was another limitation for ensuring representativeness. The HRQoL is a relevant but complex and dynamic concept. Different individuals can assess their QoL differently in the same living conditions. Nevertheless, our results may increase healthcare providers' understanding of the long-term effects of MIE on QoL in EC survivors. It could increase awareness about long-term supportive care needs, such as tailored nutritional advice, referral to cancer rehabilitation, and psycho-oncological counselling to address these patients' unmet care needs. Our findings can help to identify patients at a higher risk for a poor long-term HRQoL. Appropriate guidance can optimise their HRQoL. Further research should focus on prospective multicentre studies to determine if and when the HRQoL returns to a level comparable to the general population.

Conclusion

This study suggests that despite long-term functional, nutritional and gastrointestinal complaints, EC survivors can reach high global health status and QoL at least one year after MIE. The results suggest the need for long-term tailored support concerning nutrition, psychological rehabilitation and efficient communication.

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Statement of Ethics: A written informed consent has been obtained from participants (or their parent/legal guardian/next of kin) to participate in the study and the procedures followed were with the ethical standards of the ethical committee of Ghent University hospital and with the Helsinki declaration of 1975, as revised in 1983. The study protocol was reviewed and approved by the Ghent University hospital Ethics committee (B670201940737).

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Conceptualization: Elke Van Daele, Eva Pape.
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Manuscript revising: Elke Van Daele, Eefje Stuer, Wim Ceelen, Eva Pape.
All authors have contributed significantly conception, the acquisition, analysis, or interpretation of data for the work. All have contributed to the drafting or revising of the intellectual content of the article. All authors have read and approved the final version of the manuscript and agreed to be accountable for his/her contributions of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Data Availability Statement: The data that support the findings of this study are not publicly available based on legal grounds (their containing information that could compromise the privacy of research participants) but are available through the corresponding author EVD upon reasonable request.

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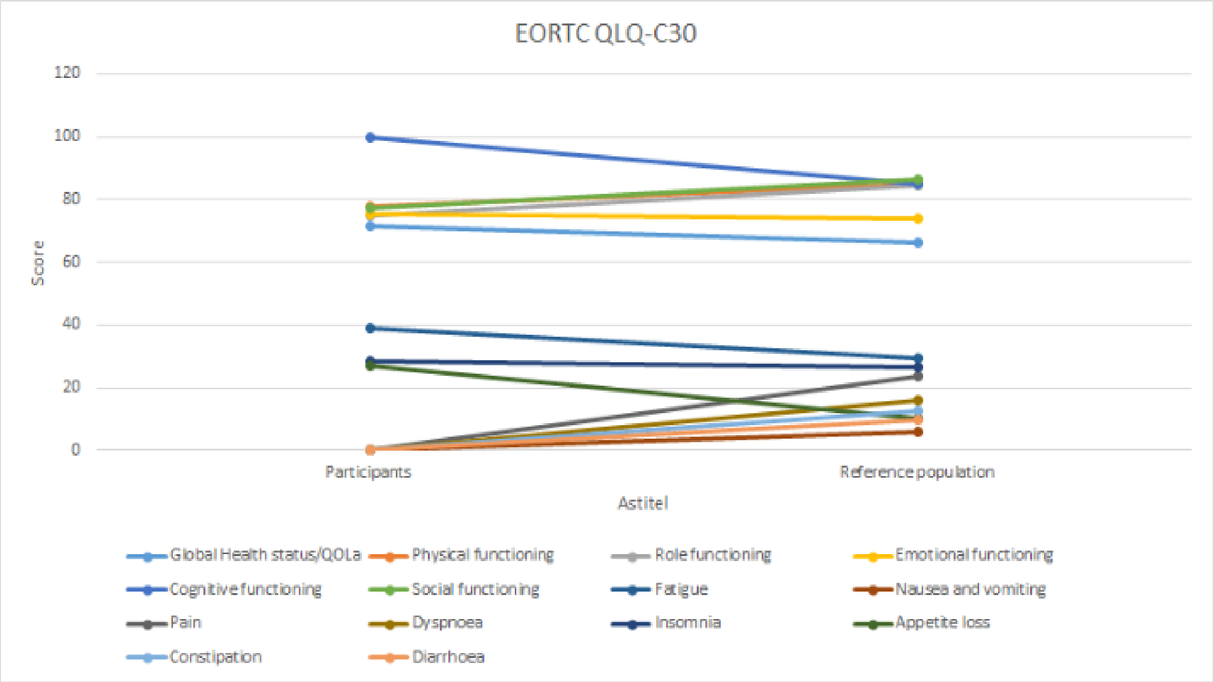
Figure Legend

Figure 1: EORTC QLQ-C30 scores of patients after minimally invasive esophagectomy compared to a reference population.

Figure 2: EORTC QLQ-OG25 scores of patients after minimally invasive esophagectomy compared to a reference population.


EORTC QLQ-C30
Score
120
100
80
60
40
20
0
Participants
Reference population
Astitel
Global Health status/QOLa
Physical functioning
Role functioning
Emotional functioning
Cognitive functioning
Social functioning
Fatigue
Nausea and vomiting
Pain
Dyspnoea
Insomnia
Appetite loss
Constipation
Diarrhoea

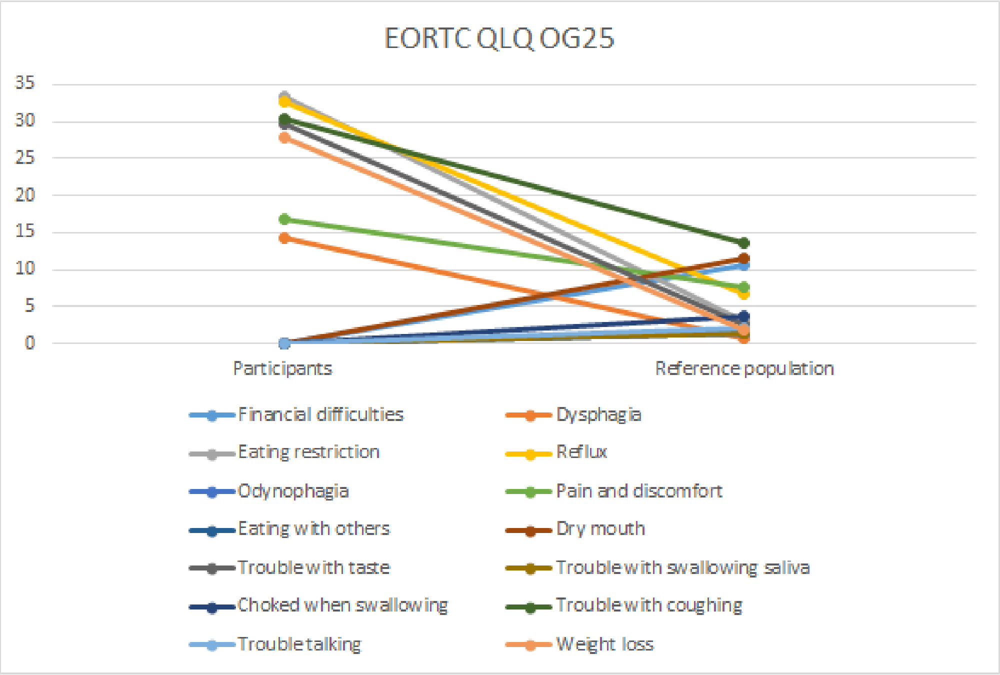

EORTC QLQ OG25
35
30
25
20
15
10
5
0
Participants
Reference population
Financial difficulties
Dysphagia
Eating restriction
Reflux
Odynophagia
Pain and discomfort
Eating with others
Dry mouth
Trouble with taste
Trouble with swallowing saliva
Choked when swallowing
Trouble with coughing
Trouble talking
Weight loss

Table 1

	Participants	**Reference population**	
	Mean (± SD)/Median (IQR)	**Mean (± SD)**	**p-value**
EORTC QLQ-C30 (vs 3)	**n = 49**	**n = 11 343**	
Global Health status/QOL[a]	71.5 ± 15.1	66.1 ± 21.7	0.016
Functional scales[a]			
Physical functioning	77.6 ± 20.0	85.1 ± 18.9	0.012
Role functioning	75.0 ± 28.4	84.3 ± 24.6	0.028
Emotional functioning	75.6 ± 24.8	74.2 ± 24.7	0.69
Cognitive functioning	100 (66.7-100)	84.8 ± 21.3	0.38
Social functioning	77.2 ± 22.7	86.2 ± 24.1	0.008
Symptom scales/items[b]			
Fatigue	39.1 ± 27.9	29.5 ± 25.5	0.021
Nausea and vomiting	0 (0-16.7)	5.9 ± 16.0	0.017
Pain	0 (0-16.7)	23.5 ± 27.1	0.007
Dyspnoea	0 (0-33.3)	15.9 ± 24.6	0.003
Insomnia	28.5 ± 32.2	26.6 ± 30.3	0.69
Appetite loss	27.1 ± 30.5	10.0 ± 21.6	< 0.001
Constipation	0 (0-33.3)	12.5 ± 23.3	0.59
Diarrhoea	0 (0-33.3)	9.5 ± 20.9	0.008
Financial difficulties	0 (0-33.3)	10.6 ± 23.6	0.58
EORTC QLQ-OG25	**n = 49**	**n = 4910**	
Symptom scales/items[b]			
Dysphagia	14.3 ± 17.7	0.8 ± 5.5	< 0.001
Eating restriction	33.3 ± 27.0	2.9 ± 9.9	< 0.001
Reflux	32.7 ± 29.7	6.7 ± 15.4	< 0.001
Odynophagia	0 (0-33.3)	1.5 ± 8.2	0.035
Pain and discomfort	16.7 (0-33.3)	7.6 ± 16.9	< 0.001
Anxiety	36.1 ± 31.4	/	/
Eating with others	0 (0-33.3)	1.3 ± 8.9	0.59
Dry mouth	0 (0-33.3)	11.5 ± 23.0	0.017
Trouble with taste	29.7 ± 35.3	2.6 ± 12.5	< 0.001
Trouble with swallowing saliva	0 (0-0)	1.3 ± 9.2	0.08
Choked when swallowing	0 (0-33.3)	3.7 ± 13.1	0.13
Trouble with coughing	30.5 ± 26.8	13.7 ± 23.6	< 0.001
Trouble talking	0 (0-0)	2.2 ± 11.0	0.09
Weight loss	27.8 ± 31.0	1.8 ± 10.5	< 0.001
Hair loss	0 (0-0)	/	/
Body image	0 (0-33.3)	/	/

Table 1: Mean and median scores of EORTC QLQ-C30 (version 3) and EORTC QLQ-OG25 of patients after minimally invasive esophagectomy compared to a reference population.

(a) Scoring range from 0 to 100. Higher scores indicate better quality of life or level of functioning. (b) Scoring range from 0 to 100. Higher scores indicate more symptoms.
Abbreviations: SD: standard deviation; IQR: interquartile range (first and third quartiles).

Table 2

Domain[a]	**Mean ± SD/ Median (IQR)**
Physical & daily living	27.85 ± 26.27
Psychological	30.08 ± 25.10
Sexuality	0 (0 – 33.33)
Patient care and support	22.34 ± 24.60
Health system & information	29.59 ± 25.55

Table 2: Mean and median scores of the SCNS-SF34 of patients after minimally invasive esophagectomy.

(a) Scoring range from 0 to 100. Higher scores indicate a higher need for supportive care.
Abbreviations: SD: standard deviation; IQR: interquartile range (first and third quartiles).