



Influence of postoperative complications following esophagectomy for cancer on quality of life: A European multicenter study



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ABSTRACT

Introduction: Postoperative complications following major surgery have been shown to be associated with reduced health-related quality of life (HRQL), and severe complications may have profound negative effects. This study aimed to examine whether long-term HRQL differs with the occurrence and severity of complications in a European multicenter prospective dataset of patients following esophagectomy for cancer.

Methods: Disease-free patients following esophagectomy for cancer between 2010 and 2016 from the LASER study were included. Patients completed the LASER, EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires >1 year following treatment. Long-term HRQL was compared between patients with and without postoperative complications, subgroup analysis was performed for severity of complications (no, minor [Clavien-Dindo I-II], severe [Clavien-Dindo \geq III]), using univariable and multivariable regression.

Results: 645 patients were included: 283 patients with no, 207 with minor and 155 with severe complications. Significantly more dyspnea (QLQ-C30) was reported by patients with compared to patients without complications (*difference in means* 6.3). In subgroup analysis, patients with severe complications reported more dyspnea (*difference in means* 8.3) than patients with no complications. None of the differences were clinically relevant (*difference in means* \geq 10 points). LASER-based low mood (OR2.3) was statistically different for minor versus severe complications.

Conclusion: Comparable HRQL was found in patients with and without postoperative complications following esophagectomy for cancer, after a mean follow-up of 4.4 years. Furthermore, patients with different levels of severity of complications had comparable HRQL. The level of HRQL in esophageal cancer patients are more likely explained by the impact of the complex procedure of the esophagectomy itself.

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1. Introduction

The incidence of esophageal cancer is increasing globally, with

over 600.000 esophageal cancer patients diagnosed in 2020 [1]. After curative treatment, usually consisting of neoadjuvant chemo(radio)therapy and esophagectomy with lymphadenectomy, the current 5-year survival rate reaches almost 50% [2–6]. Postoperative complications after esophageal cancer surgery remain a major concern, as in over 50% of the patients complications occur, of which over 17% of patients have severe complications, requiring surgical intervention under general anaesthesia (Clavien-Dindo \geq IIIb) [7]. Postoperative complications are associated with increased postoperative mortality and decreased long-term

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Abbreviations

EORTC	European Organization for Research and Treatment of Cancer
HRQL	Health related quality of life
LASER	Lasting Symptoms After Esophageal Resection
IQR	Interquartile range
CI	Confidence Interval

survival [8–10]. Studies investigating the relation between the occurrence of complications following major surgery and health-related quality of life (HRQL) show that complications are negatively associated with short- and long-term HRQL [10–16]. A multicenter longitudinal study with a total of 785 patients following major elective gastrointestinal, cardiothoracic, or vascular surgery found severe complications to be associated with significantly impaired short-term HRQL [11]. Several other studies also found postoperative complications following an esophagectomy to be negatively associated with HRQL [10,14,17,18]. One of these studies found that severe complications are associated with a long-lasting poor HRQL. Patients who endured major postoperative complications reported significantly more problems with dyspnea and fatigue compared to patients without any major postoperative complications [10]. However in a recent population-based study including 486 Dutch patients after an esophagectomy, no significant differences were found in short- and long-term HRQL between patients with and without complications [19]. None of these studies analysed HRQL according to the severity of postoperative complications, using a complication grading system, such as the Clavien-Dindo classification in an international group of patients [20,21].

Therefore the primary aim of this study was to examine whether long-term HRQL differs with the occurrence and severity of postoperative complications in a European multicenter prospective dataset of esophagectomy patients (LASER study) [22]. We hypothesized that the severity of postoperative complications are proportionally negatively associated with long-term HRQL: patients with severe complications are likely to have significantly worse long-term HRQL compared to patients with no or minor postoperative complications.

2. Methods

2.1. The Lasting Symptoms After Esophageal Resection (LASER) study database

The LASER study is a prospective European multicenter cross-sectional study, which aimed to identify symptoms with the highest incidence and the greatest impact on HRQL in disease-free patients following an esophagectomy for esophageal or gastroesophageal junction cancer [22]. The primary study outcomes of the LASER study have been published before [22]. Ethical approval to use the LASER study dataset for side studies were gained by each participating centre during the original LASER study, and written informed consent was signed by all participants to use their data in retrospective studies.

The STROBE guidelines were followed to ensure the correct structure in this article [23].

This current multicenter population-based prospective comparative cohort study was performed with the data from the Lasting Symptoms After Esophageal Resection (LASER) study database [22]. Patients who underwent a curative intent

esophagectomy in one of the 20 participating centers across Europe, between January 1, 2010 and June 30, 2016, and were disease-free and at least 1 year post completion of treatment were eligible for inclusion and invited to participate. Eligible patients completed three questionnaires, solely once (The European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30 and EORTC QLQ-OG25 HRQL questionnaires and the LASER symptom questionnaire) [22,24]. Exclusion criteria for this study were missing clinical and treatment data, and missing Clavien-Dindo categorization.

2.2. Patient, tumor and complications characteristics

The following characteristics were collected; age (years), sex (male/female), neoadjuvant treatment (yes/no), time since surgery (years) adjuvant treatment (yes/no), country wherein procedure was performed, surgical technique (Ivor Lewis, McKeown, transhiatal and left thoracoabdominal), surgical access (minimally invasive esophagectomy [MIE], hybrid and open), anastomotic site (cervical or intrathoracic), pathological tumor stage (0, I, II, III-IV) and tumor subtype (adenocarcinoma and squamous cell carcinoma).

Complications were recorded according to the ECCG criteria (Supplementary Table S1) and graded using the Clavien-Dindo grading system [20,21,25]. Patients were first divided into subgroups according to the presence of post-operative complications, i.e., those with or without postoperative complications. They were secondly divided according to the severity of post-operative complications, i.e., those with no, minor (Clavien-Dindo grade I-II) or severe (Clavien-Dindo grade \geq III postoperative complications) [7,20,21].

2.3. Questionnaires

2.3.1. EORTC quality of life questionnaires

The EORTC QLQ-C30 is validated for all cancer patients and consist of 30 questions [24]. Response options range from 1 to 7 ('very poor'-'excellent') for two questions and from 1 to 4 ('not at all', 'a little', 'quite a bit' and 'very much') in the remaining 28 questions. These items are combined to form 15 outcomes as follows: six multiple-item scales (global health, physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), and five additional single items assessing symptoms often reported by cancer patients (dyspnea, insomnia, appetite loss, constipation and diarrhea) and finally financial difficulties.

The EORTC QLQ-OG25 is recommended to supplement the QLQ-C30 when assessing the HRQL in patients with esophageal, junctional or gastric cancer. It includes 25 questions with answers ranging from 1 to 4 ('not at all', 'a little', 'quite a bit' and 'very much') [26]. From this questionnaire, a total of 16 HRQL domains are assessed. The domains are subdivided into six multi-item scales (dysphagia, eating restrictions, reflux, odynophagia, pain and discomfort, and anxiety) and 10 single-items (eating with others, dry mouth, trouble with taste, body image, trouble swallowing saliva, choked when swallowing, trouble with coughing, trouble talking, weight loss and hair loss).

The 31 HRQL domain scores derived from both questionnaires are linearly transformed into scores ranging from 0 to 100. Higher mean scores in global health and functioning domains represent better HRQL. In symptom domains, a higher mean score represents more symptomatology.

The LASER questionnaire was developed by the LASER study group, to appoint symptoms associated with esophagectomy experienced in the past 6 months [22]. The questionnaire assesses

among other things 28 symptoms associated with esophagectomy. These LASER symptoms are graded according the impact upon quality of life ('none', 'some', and 'substantial') and frequency of symptoms, scoring from 0 to 5 ('never', 'rarely', 'weekly', 'daily' and 'multiple times per day'). In the LASER study, the following three LASER symptoms were found to be associated with poor HRQL as measured by the EORTC QLQ-C30 and QLQ-OG25; pain on scars on chest, low mood and reduced energy or activity tolerance. These symptoms will be referred to as LASER key symptoms and will be investigated in this study [22]. (Appendix A).

2.4. Statistical analysis

Descriptive statistics summarized the patient, tumor and treatment characteristics of the included patients. Continuous variables are noted as means with standard deviation or medians and interquartile ranges (IQR). Categorical variables were noted with percentage frequencies.

Univariable and multivariable linear regression analyses were performed for the analysis of the differences in HRQL domain scores (EORTC QLQ-C30 and QLQ-OG25) between patients 'with' and patients 'without' complications with adjustment for the confounders; age, sex, neoadjuvant treatment, years since surgery, surgical technique, surgical access, anastomotic site, pathological tumor stage and tumor subtype. HRQL domain scores were entered in the multivariable analysis if a p-value of <0.10 was reached in univariable analysis. Univariable and multivariable pairwise subgroup analyses were also performed according to severity of complications between patient with minor versus no, severe versus no, and minor versus severe

postoperative complications. Mean scores with 95% confidence intervals (95%CI) were calculated and were compared between groups. Statistical significance was tested using the Student's *t*-test. A p-value of <0.01 was considered to be statistically significant.

For LASER key symptoms odds ratios adjusted for above mentioned confounders were calculated with a 95%CI using logistic regression models. To reduce the type-1 error due to multiple comparisons, statistical significance only tested if adjusted mean score difference was of clinical relevance [27–29]. A p-value of <0.05 was considered to be statistically significant.

Additionally, subgroup analyses were performed to examine whether HRQL differs with the occurrence and severity of postoperative complications over time. These analyses and results can be found supplement I.

In this study, a mean score difference in HRQL score of 10 or more points was considered clinically relevant. Whereas the minimally important change in mean scores varies across HRQL domains, a cut-off point of 10 points is most likely the upper bound for most domains [24,27].

Data was handled anonymously and the statistical analysis were conducted by a biostatistician (A.J.) with SAS 9.4 software.

3. Results

3.1. Patient, tumor and complication characteristics

A total of 645 patients from the LASER dataset were included for analysis in this study. The response rate in the LASER study was 81%: 876 of 1081 invited patients. Two hundred thirty-one patients

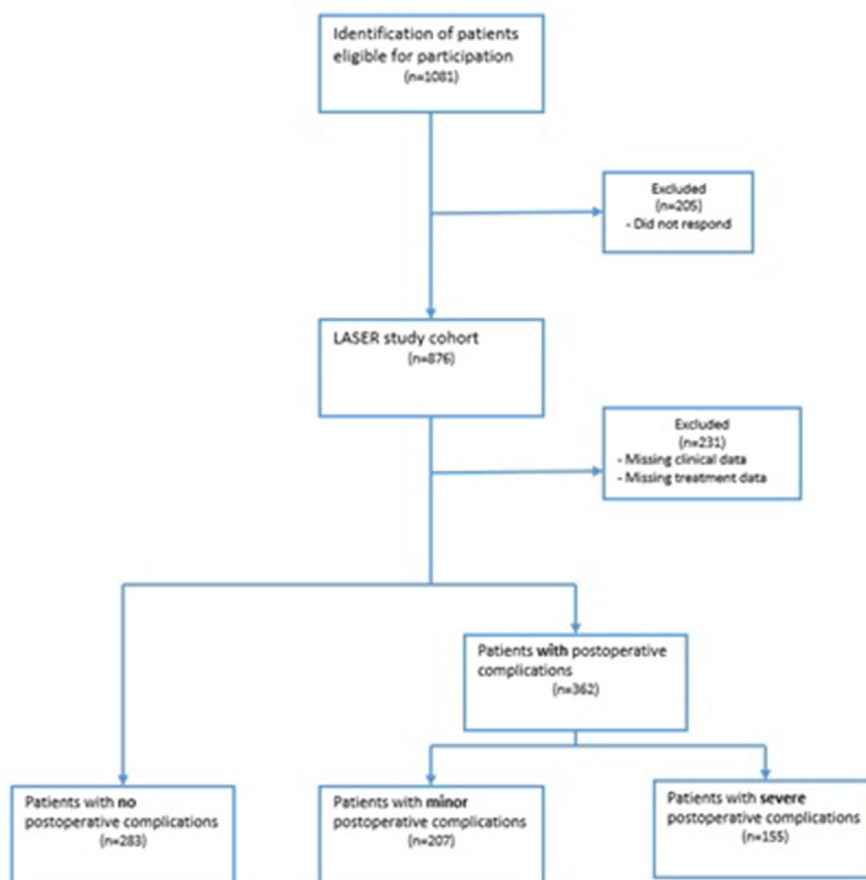


Fig. 1. Study flow chart of patient inclusion.

were excluded from analyses in this study: 154 patients did not have available clinical and/or treatment data, and 77 patients had no available Clavien–Dindo categorization (Fig. 1).

The majority of the remaining patients included in this study were male (78%), the mean age was 64 years (SD 9). Most patients (79%) received neoadjuvant therapy and 14% received adjuvant therapy. The most frequently performed surgical procedure was an Ivor-Lewis esophagectomy (54%), followed by a McKeown (25%).

Postoperative complications occurred in 56% of the patients, 283 patients (44%) did not have any postoperative complications, 207 patients (31%) had minor postoperative complications and 155 patients (24%) had severe postoperative complications. The three most frequently occurring complications were pulmonary complications (27%), cardiac complications (14%) and anastomotic leakage (12%). The mean time since surgery was 4.4 years (SD 1.7). All patient, tumor and complication characteristics can be found in Table 1.

3.2. Patients ‘with’ and ‘without’ postoperative complications

For HRQL domains global health, physical functioning, role functioning, social functioning, pain, dyspnea, appetite loss, reflux,

Table 1

Baseline characteristics of patients with ‘no’, ‘minor’ and ‘severe’ postoperative complications following and esophagectomy for esophageal or junctional cancer.

	Total		‘No’ postoperative complications		‘Minor’ postoperative complications		‘Severe’ postoperative complications	
	N = 645		N = 283		N = 207		N = 155	
Age (mean [SD], y)	64	9.1	63.7	8.9	64.3	9.2	63.6	9.3
Years since surgery (mean, [SD],y)	4.4	1.7	4.5	1.7	4.5	1.8	4.3	1.6
Gender	502	78%	216	76%	169	82%	117	75%
Neoadjuvant therapy	508	79%	236	83%	150	72%	122	79%
	137	21%	47	17%	57	28%	33	21%
Adjuvant therapy	92	14%	51	18%	26	13%	15	10%
	486	75%	198	70%	163	79%	125	81%
	67	10%	34	12%	18	9%	15	10%
Complications	174	27%	–	–	82	40%	92	60%
	89	14%	–	–	52	25%	37	24%
	74	11%	–	–	24	12%	50	32%
	50	8%	–	–	15	7%	35	23%
	22	3%	–	–	10	5%	12	8%
	22	3%	–	–	10	5%	12	8%
	59	9%	–	–	32	15%	27	17%
	14	2%	–	–	2	1%	12	8%
	33	5%	–	–	19	9%	14	9%
	8	1%	–	–	–	1%	5	3%
	49	8%	–	–	19	9%	30	19%
	27	4%	–	–	9	4%	18	12%
	13	2%	–	–	–	–	13	8%
Country	209	33%	86	41%	77	37%	46	22%
	171	27%	84	49%	37	22%	50	29%
	66	10%	19	29%	24	36%	23	35%
	27	4%	11	41%	11	41%	5	19%
	67	10%	46	69%	12	18%	9	13%
	75	12%	18	24%	42	56%	15	20%
	28	4%	17	61%	4	24%	7	25%
Surgical technique	351	54%	168	48%	106	30%	77	22%
	33	5%	21	64%	5	15%	7	21%
	162	25%	47	29%	62	38%	53	33%
	99	15%	47	47%	34	34%	18	18%
Surgical access	110	17%	52	47%	29	26%	29	26%
	188	29%	93	49%	60	32%	35	19%
	347	54%	138	40%	118	34%	91	26%
Location anastomosis	257	40%	93	36%	98	38%	66	26%
	388	60%	190	49%	109	28%	89	23%
Pathological stage	133	21%	52	18%	45	22%	36	23%
	210	33%	81	29%	70	34%	59	38%
	159	25%	66	23%	54	26%	39	25%
	143	22%	84	30%	38	18%	21	14%

Data are presented as n (%) unless otherwise indicated. IQR = interquartile range. SD = standard deviation. y = year. Kg = kilograms. MIE = minimal invasive esophagectomy. c/(y)pTNM tumor staging classification. Minor postoperative complications defined as Clavien–Dindo grade I–II, severe postoperative complications defined as Clavien–Dindo ≥ III. Percentages may not add up due to rounding.

pain and discomfort, and weight loss a p-value of <0.10 was found after univariable linear regression analysis. In multivariable analysis, significantly more dyspnea was found in patients with postoperative complications than in patients without postoperative complications (difference in means 6.26, p < 0.01) (Table 2, Fig. 2). However, this result was not clinically relevant (difference in means < 10 points) nor were the results of any other outcome of the EORTC QLQ-C30 and QLQ-OG25.

For the three LASER key symptoms, none of the odds ratios in the univariable analysis were statistically significant nor reached the threshold to perform multivariate analysis (Table 3).

3.3. Patients with ‘no’, ‘minor’ and ‘severe’ postoperative complications

After univariable linear regression analysis of all the HRQL domains, patients with minor postoperative complications reported higher levels of dyspnea (difference in means 6.8, p 0.006) and appetite loss (difference in means 7.5, p 0.003) than patients with no postoperative complications.

Patients with severe complications reported more dyspnea

Table 2
Univariable and multivariable linear regression analysis of HRQL comparing patients 'with' and patients 'without' postoperative complications.

	Without complications Mean (95% CI) n = 283	With complications LS Mean (95% CI) n = 362	Univariable analysis			Multivariable analysis [^]				
			Difference in means	95%CI		p-value	Difference in means	95%CI		p-value
				Lower	Upper			Lower	Upper	
EORTC QLQ-C30										
Global Health	74.2 (71.8–76.6)	71.1 (69.0–73.3)	-3.1	-6.3	0.2	0.06*	-2.8	-6.4	0.7	0.12
Functioning										
Physical functioning	83.9 (81.8–86.0)	81.3 (79.4–83.2)	-2.6	-5.4	0.3	0.07*	-2.5	-5.6	0.5	0.11
Role functioning	82.4 (79.4–85.4)	78.9 (76.3–81.6)	-3.5	-7.5	0.6	0.09*	-2.5	-7.0	1.9	0.27
Emotional functioning	81.2 (78.6–83.9)	81.4 (79.1–83.7)	0.2	-3.3	3.7	0.92				
Cognitive functioning	82.3 (79.8–84.7)	83.9 (81.7–86.0)	1.6	-1.6	4.9	0.32				
Social functioning	83.0 (80.0–85.9)	78.5 (76.0–81.1)	-4.4	-8.4	-0.5	0.03*	-3.6	-7.7	0.6	0.09
Symptom scores										
Fatigue	28.3 (25.4–31.3)	31.6 (29.0–34.1)	3.2	-0.7	7.1	0.10				
Nausea and vomiting	12.1 (9.9–14.3)	13.4 (11.5–15.4)	1.3	-1.7	4.3	0.39				
Pain	13.4 (10.8–16.0)	16.3 (14.1–18.6)	3.0	-0.5	6.4	0.09*	1.7	-2.0	5.4	0.37
Dyspnea	17.0 (13.8–20.1)	25.0 (22.2–27.7)	8.0	3.8	12.2	<0.001*	6.3	1.8	10.8	<0.01
Insomnia	23.4 (20.0–26.7)	22.3 (19.4–25.3)	-1.0	-5.5	3.4	0.64				
Appetite loss	14.3 (11.1–17.5)	20.6 (17.7–23.4)	6.3	2.0	10.6	<0.05*	6.0	1.3	10.7	0.01
Constipation	12.4 (10.0–14.9)	11.7 (9.5–13.9)	-0.7	-4.0	2.6	0.68				
Diarrhea	16.7 (13.9–19.6)	19.3 (16.8–21.8)	2.6	-1.3	6.4	0.19				
Financial										
Financial difficulties	13.2 (10.1–16.3)	13.1 (10.4–15.8)	-0.1	-4.2	4.1	0.97				
EORTC QLQ-OG25										
Multi-item										
Dysphagia	10.6 (8.7–12.4)	8.8 (7.2–10.5)	-1.7	-4.2	0.8	0.18				
Eating restrictions	21.7 (19.1–24.3)	23.9 (21.6–26.2)	2.2	-1.3	5.7	0.22				
Reflux	28.6 (25.5–31.8)	24.9 (24.9–22.1)	-3.7	-8.0	0.5	0.08*	-4.1	-8.8	0.5	0.08
Odynophagia	11.2 (9.1–13.3)	11.2 (9.3–13.0)	-0.00	-2.8	2.8	0.99				
Pain and discomfort	16.2 (13.5–18.9)	19.6 (17.2–21.9)	3.4	-0.2	7.0	0.06*	1.1	-2.7	4.9	0.56
Anxiety	28.5 (25.3–31.8)	29.5 (26.6–32.3)	0.9	-3.4	5.3	0.68				
Single Item										
Eating with others	13.0 (10.2–15.7)	10.5 (8.1–13.0)	-2.4	-6.1	1.2	0.19				
Dry mouth	21.8 (18.4–25.2)	22.8 (18.8–25.8)	1.0	-3.5	5.6	0.66				
Trouble with taste	14.9 (12.1–17.8)	12.3 (9.7–14.8)	-2.7	-6.5	1.1	0.17				
Body image	13.0 (10.0–16.1)	15.2 (12.5–17.9)	2.2	-1.9	6.2	0.29				
Trouble swallowing saliva	6.9 (5.0–8.8)	5.3 (3.6–7.0)	-1.6	-4.1	1.0	0.23				
Choked when swallowing	10.8 (8.5–13.2)	11.1 (9.0–13.2)	0.3	-2.9	3.4	0.86				
Trouble with coughing	28.4 (25.1–31.6)	30.3 (27.4–33.2)	1.9	-2.4	6.3	0.38				
Trouble talking	10.5 (8.2–12.8)	9.0 (7.0–11.1)	-1.5	-4.6	1.6	0.35				
Weight loss	16.1 (12.6–19.5)	19.9 (16.9–23.0)	3.9	-0.7	8.5	0.09*	3.2	-1.9	8.3	0.21
Hair loss	26.8 (25.1–28.4)	25.4 (24.0–26.9)	-1.3	-3.5	0.9	0.23				

Difference in between means with 95% confidence interval (CI) are shown for univariable and multivariable analysis.

[^] = corrected for confounders. * = Health related quality of life (HRQL) domains with p-value <0.1 in univariable analysis were entered in multivariable analysis.

In bold values that were statistically significant. (p-value < 0.01). Patients without postoperative complications defined as not having experienced any complications post-operatively. Patient with complications defined as having experienced any postoperative complications (Clavien-Dindo ≥ 1).

(difference in means 9.6, p < 0.001) compared to patients with no postoperative complications.

No statistically significant difference in mean scores was found for patients with minor postoperative complications compared to patients with severe postoperative complications (Table 4 [domains with statistically significant differences], Supplementary Table S2 and Supplementary Fig. S1 [all domains]).

For the domains entered in the multivariable analysis the patients with severe postoperative complications reported more dyspnea (difference in means 8.3, p < 0.01) compared to patients with no postoperative complications (Supplementary Table S3).

However, none of the differences for any of the 31 HRQL domains between any of the severity groups after univariable or multivariable regression analysis was found to reach the threshold

for clinical relevance.

For patients with minor versus no postoperative complications the odds ratio for LASER key symptoms reduced energy and activity tolerance (OR 1.5, p 0.05) was statistically significant.

For patients with minor versus severe postoperative complications the odds ratio for LASER key symptoms low mood (OR 2.5, p 0.02) and reduced energy and activity tolerance (OR 1.6, p 0.04) were statistically significant.

For patient with severe versus no, none of the OR found for the LASER key symptoms differed significantly (Table 5).

After multivariable regression the found odds ratio for LASER key symptoms low mood (OR 2.3, p 0.04), for minor versus severe postoperative complications remained statistically significant (Supplementary Table S4).

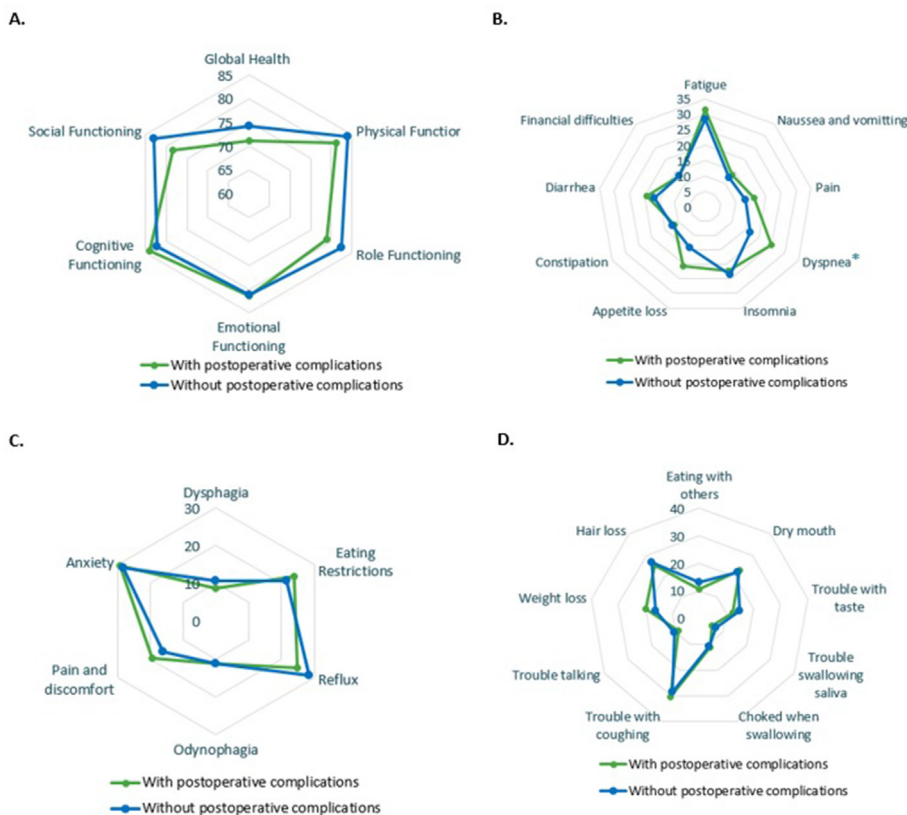


Fig. 2. Spider plots showing domain outcome scores for patients with (green line) and patients without (blue line) postoperative complications. Higher scores in global health and functioning domains represent better HRQL. In symptom domains, a higher score represents more symptomatology. The asterisk indicates a significant difference ($p < 0.01$) between patient with and patients without postoperative complications within a HRQL domain. A: EORTC QLQ-C30 Global health and functioning domains, B: EORTC QLQ-C30 symptom and financial domains, C: EORTC QLQ-OG25 Multi-item domains, D: EORTC QLQ-OG25 Single-item domains.

4. Discussion

This study investigated whether long-term HRQL was associated with postoperative complications in disease-free patients following an esophagectomy for distal esophageal or gastroesophageal junction cancer after a follow-up of at least one year post completion of therapy. The results of this study show, that in general, long-term HRQL does not differ between patients with and without postoperative complications, nor between patients with different grades in severity of postoperative complications. Although the symptom dyspnea differed statistically significantly after multivariate analysis between patients with and without postoperative complications, and between patients with severe and

Table 3

Univariable analysis of the LASER key symptoms comparing patients ‘with’ and patients with ‘no’ postoperative complications.

LASER key symptoms	Univariable analysis	
	Odds ratio (95% CI)	p-value
Pain from scars on your chest	1.251 (0.597–2.622)	0.5532
Low mood	0.997 (0.597–1.666)	0.9913
Reduced energy/activity tolerance	1.212 (0.863–1.702)	0.2678

Odds ratio comparing patients with and without complications with 95% confidence interval (CI) are shown for univariable analysis. None of odds ratios had a p-value < 0.1 in univariable analysis therefore no multivariable analysis were performed. Patients without postoperative complications defined as not having experienced any complications postoperatively. Patient with complications defined as having experienced any postoperative complications (Clavien-dindo ≥ 1).

no postoperative complications, this was not a clinically relevant difference (difference in means < 10 points). The other statistically significant finding in this study was that patients with minor postoperative complications reported more often the LASER key symptom low mood than patients with severe postoperative complications. These findings run counter to our hypothesis as we had expected that the presence and the severity of postoperative complications are proportionally negatively associated with long-term HRQL. A possible explanation could be, that in this current study, HRQL was measured at a mean of 4.4 years after treatment. Earlier studies have shown, that the postoperative reduction in HRQL in disease-free patients restores to baseline within one to two years after esophagectomy [19,30,31]. However other studies report a negative effect of major postoperative complications to last more than 5 years. In the study by Kauppila et al. the impact of an esophagectomy with postoperative complications was found to be associated with an impaired HRQL up to 10 years after esophagectomy [14]. In the study of Derogar et al. evaluating the influence of major postoperative complications on HRQL in 5-year survivors of esophageal cancer surgery, patients with major postoperative complications reported more problems, that are clinically relevant and statistically significant, for appetite loss, fatigue and dyspnea at 6-months, 3 years and 5 years compared to patients without postoperative complications [10]. Comparable with our results is that significant more symptomatology was reported for dyspnea by patients with severe postoperative complications, in our study this difference was not clinically relevant. In this current study, only disease-free patients, who were free from surgical complications at the time of assessment were included compared

Table 4

Statistically significant differences in HRQL after univariable analysis comparing patients with minor versus no, severe versus no and severe versus minor postoperative complications.

	'Minor' postoperative complications n = 207	'Severe' postoperative complications n = 155	'No' postoperative complications n = 283	Minor vs No			Severe vs No			Severe vs Minor		
				Difference in means	95% CI Lower Upper		p-value	Difference in means	95% CI Lower Upper		p-value	Difference in means
EORTC QLQ-C30	Mean	Mean	Mean									
Global Health	70.3	72.1	74.2	-3.8	-7.6	-0.1	0.04*	-	-	-	-	-
Functioning												
Social functioning	78.3	78.8	83.0	-4.7	-9.2	-0.2	0.04*	-	-	-	-	-
Symptom scores												
Dyspnea	23.7	26.6	17.0	6.8	2.0	11.6	<0.01*	9.6	4.4	14.9	<0.01*	-
Appetite loss	21.8	19.0	14.3	7.5	2.6	12.5	<0.01*	-	-	-	-	-

Difference in between means with 95% confidence interval (CI) are shown for univariable analysis.

In bold values that were statistically significant (p-value < 0.01). * = domains with p-value < 0.1 in univariable analysis were entered in multivariable analysis.

'Minor' postoperative complications defined as Clavien-Dindo grade I-II, 'severe' postoperative complications defined as Clavien-Dindo ≥ III.

Table 5

Univariable analysis of the LASER key symptoms comparing for severity of postoperative complications.

	Minor vs No		Severe vs No		Minor vs Severe	
	Odds ratio	p-value	Odds ratio (95%CI)	p-value	Odds ratio	p-value
Pain from scars on your chest	0.91 (0.36–2.26)	0.84	1.73 (0.74–4.01)	0.20	0.53 (0.21–1.34)	0.18
Low mood	1.37 (0.79–2.38)	0.26	0.54 (0.25–1.17)	0.12	2.54 (1.16–5.55)	<0.05#
Reduced energy and activity tolerance	1.47 (1.00–2.16)	<0.05#	0.91 (0.59–1.42)	0.68	1.61 (1.02–2.54)	<0.05#

Odds ratio comparing patients with 'Minor' vs 'Severe', 'Minor' vs 'No', and 'Severe' vs 'No' postoperative complications with 95% confidence interval (CI) are shown for univariable analysis.

= LASER key symptoms with p-value < 0.1 in univariable analysis were entered in multivariable analysis. In bold values that were statistically significant. (p-value < 0.05).

'Minor' postoperative complications defined as Clavien-Dindo grade I-II, 'severe' postoperative complications defined as Clavien-Dindo ≥ III.

to all patients who survived for 5 or more years after curative surgery in the prospective study by Derogar [10]. Therefore the found differences could be less pronounced in our study, since patients with more severe complications may not have been included, due to ongoing postoperative complications or due to early death, which may lead to more fit patients in our study cohort with better HRQL.

Several limitations of our study merit attention. This study has a cross-sectional design. We therefore do not know the baseline HRQL nor the baseline patient characteristics. Moreover, we cannot report changes in these scores over time. The follow-up varies from 1 year to 8 years, and there might be intra-individual difference over time but due to the cross-sectional design of this study and the one-time assessment of the questionnaires, this could not be investigated. The study may have been prone to non-response bias and selection bias, as it only includes patients who were disease-free and at least one year following surgery. Patients who died, had recurrence of the disease, and patient who refused to participate in the study were not included in the analysis, which may have led to a bias towards patients with relatively more positive HRQL levels. The reason for patients declining participation was not recorded. Furthermore, in the LASER questionnaire, patients were asked to appoint symptoms experienced in the last 6 months, this might have led to recall bias. The EORTC QLQ-C30 and QLQ-OG25 focuses on symptoms experienced during the past week, this might have led to a snapshot of the HRQL. The number of statistical test performed was relatively high in this study, therefore to reduce the statistical probability of finding significant difference by chance, the statistical significance was only tested if adjusted mean score difference was of clinical relevance and a probability value of less than 0.01 was used.

This study also has several strengths. It employed a large sample size of patients who underwent an esophagectomy in 20 European centers. Most of the included patients were treated with neoadjuvant therapy. Therefore, our study reflects the current treatment practices of esophageal cancer patients in Europe and the results may be generalizable to esophageal cancer patients in other countries of Europe that adopt the same treatment practices.

There is a need of future studies employing a longitudinal design, (e.g. as in the PACAP, POCOP and PLCRC studies) [32] to enable the investigation of patterns of HRQL over time, i.e., deterioration, recovery and improvement in patients based on severity of postoperative complications. Additionally, what can be done to reduce the postoperative decline in HRQL, and what steps we can take to restore this HRQL in esophagectomy patients faster.

In conclusion, in this study comparable HRQL was found in patients with and without postoperative complications following esophagectomy for distal esophageal or gastro-esophageal cancer, after a mean of follow-up of 4.4 years. Patients with different grades of severity of complications had comparable long-term HRQL. The level of HRQL in esophageal cancer patients are more likely explained by the impact of the complex procedure of the esophagectomy itself.

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Declaration of competing interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2022.07.020>.

References

- [1] International agency for Research on cancer W. Colombia: Globocan; 2020. <https://GcolarcFr/Today/Data/Factsheets/Populations/170-Colombia-FactsheetsPdf 2020>.
- [2] Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015. [https://doi.org/10.1016/S1470-2045\(15\)00040-6](https://doi.org/10.1016/S1470-2045(15)00040-6).
- [3] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006. <https://doi.org/10.1056/nejmoa055531>.
- [4] Lagergren J, Mattsson F, Zylstra J, Chang F, Gossage J, Mason R, et al. Extent of lymphadenectomy and prognosis after esophageal cancer surgery. *JAMA Surg* 2016. <https://doi.org/10.1001/jamasurg.2015.2611>.
- [5] Hoepfner J, Zirlik K, Brunner T, Bronsert P, Kulemann B, Sick O, et al. Multimodal treatment of locally advanced esophageal adenocarcinoma: which regimen should we choose? Outcome analysis of perioperative chemotherapy versus neoadjuvant chemoradiation in 105 patients. *J Surg Oncol* 2014. <https://doi.org/10.1002/jso.23498>.
- [6] Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011. [https://doi.org/10.1016/S1470-2045\(11\)70142-5](https://doi.org/10.1016/S1470-2045(11)70142-5).
- [7] Low DE, Kuppusamy MK, Alderson D, Ceccanello I, Chang AC, Darling G, et al. Benchmarking complications associated with esophagectomy. *Ann Surg* 2019. <https://doi.org/10.1097/SLA.0000000000002611>.
- [8] Rizk NP, Bach MS, Turnbull AD, Karpeh M, Brennan MF, Rusch VW, et al. The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. *J Am Coll Surg* 2004.
- [9] Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005. <https://doi.org/10.1097/01.sla.0000179621.33268.83>.
- [10] Derogar M, Orsini N, Sadr-Azodi O, Lagergren P. Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery. *J Clin Oncol* 2012. <https://doi.org/10.1200/JCO.2011.40.3568>.
- [11] Archer S, Pinto A, Vuik S, Bicknell C, Faiz O, Byrne B, et al. Surgery,

- complications, and quality of life: a longitudinal cohort study exploring the role of psychosocial factors. *Ann Surg* 2019. <https://doi.org/10.1097/SLA.0000000000002745>.
- [12] Bloemen JG, Visschers RGJ, Truin W, Beets GL, Konsten JLM. Long-term quality of life in patients with rectal cancer: association with severe postoperative complications and presence of a stoma. *Dis Colon Rectum* 2009. <https://doi.org/10.1007/DCR.0b013e3181a74322>.
- [13] Kauppila JH, Mattsson F, Brusselselaers N, Lagergren J. Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study. *BMJ Open* 2018. <https://doi.org/10.1136/bmjopen-2018-021495>.
- [14] Kauppila JH, Johar A, Lagergren P. Postoperative complications and health-related quality of life 10 years after esophageal cancer surgery. *Ann Surg* 2020. <https://doi.org/10.1097/SLA.0000000000002972>.
- [15] Rutegård M, Lagergren J, Rouvelas I, Lindblad M, Blazeby JM, Lagergren P. Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. *Br J Surg* 2008. <https://doi.org/10.1002/bjs.6021>.
- [16] Viklund P, Lindblad M, Lagergren J. Influence of surgery-related factors on quality of life after esophageal or cardia cancer resection. *World J Surg* 2005. <https://doi.org/10.1007/s00268-005-7887-9>.
- [17] Scarpa M, Saadeh LM, Fasolo A, Alfieri R, Cagol M, Cavallin F, et al. Health-related quality of life in patients with oesophageal cancer: analysis at different steps of the treatment pathway. *J Gastrointest Surg* 2013. <https://doi.org/10.1007/s11605-012-2069-1>.
- [18] Van Der Schaaf M, Lagergren J, Lagergren P. Persisting symptoms after intrathoracic anastomotic leak following oesophagectomy for cancer. *Br J Surg* 2012. <https://doi.org/10.1002/bjs.7750>.
- [19] Jezerskyte E, van Berge Henegouwen MI, van Laarhoven HWM, van Kleef JJ, Eshuis WJ, Heisterkamp J, et al. Postoperative complications and long-term quality of life after multimodality treatment for esophageal cancer: an analysis of the prospective observational cohort study of esophageal-gastric cancer patients (POCOP). *Ann Surg Oncol* 2021. <https://doi.org/10.1245/s10434-021-10144-5>.
- [20] Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009. <https://doi.org/10.1097/SLA.0b013e3181b13ca2>.
- [21] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004. <https://doi.org/10.1097/01.sla.0000133083.54934.ae>.
- [22] Markar SR, Zaninotto G, Castoro C, Johar A, Lagergren P, Elliott JA, et al. Lasting symptoms after esophageal resection (LASER). *Ann Surg* 2020. <https://doi.org/10.1097/sla.0000000000003917>.
- [23] Vandembroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007. <https://doi.org/10.1371/journal.pmed.0040297>.
- [24] Fayers P, Aaronson N, Bjordal K. *EORTC QLQ-C30 scoring manual*. Eortc 2001.
- [25] Low DE, Alderson D, Ceconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy Complications Consensus Group (ECCG). *Ann Surg* 2015. <https://doi.org/10.1097/SLA.0000000000001098>.
- [26] Lagergren P, Fayers P, Conroy T, Stein HJ, Sezer O, Hardwick R, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-OG25, to assess health-related quality of life in patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach. *Eur J Cancer* 2007. <https://doi.org/10.1016/j.ejca.2007.07.005>.
- [27] Cocks K, King MT, Velikova G, De Castro G, Martyn St-James M, Fayers PM, 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. <https://doi.org/10.1016/j.ejca.2012.02.059>.
- [28] 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. <https://doi.org/10.1200/JCO.1998.16.1.139>.
- [29] King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996. <https://doi.org/10.1007/BF00439229>.
- [30] Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer* 2000. [https://doi.org/10.1002/\(SICI\)1097-0142\(20000415\)88:8<1781::AID-CNCR4>3.0.CO;2-G](https://doi.org/10.1002/(SICI)1097-0142(20000415)88:8<1781::AID-CNCR4>3.0.CO;2-G).
- [31] Lagergren P, Avery KNL, Hughes R, Barham CP, Alderson D, Falk SJ, et al. Health-related quality of life among patients cured by surgery for esophageal cancer. *Cancer* 2007. <https://doi.org/10.1002/cncr.22833>.
- [32] Coebergh van den Braak RRJ, van Rijssen LB, van Kleef JJ, Vink GR, Berbee M, van Berge Henegouwen MI, et al. Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative. *Acta Oncol (Madr)* 2018. <https://doi.org/10.1080/0284186X.2017.1346381>.