

BMJ Open Lymphadenectomy and health-related quality of life after oesophageal cancer surgery: a nationwide, population-based cohort study

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ABSTRACT

Objective: The purpose of this study was to clarify whether more extensive surgical lymph node resection during oesophageal cancer surgery influences patients' health-related quality of life (HRQOL).

Setting: This was a nationwide Swedish population-based study.

Participants: A total of 616 patients who underwent curatively intended oesophageal cancer surgery in 2001–2005 were followed up at 6 months and 5 years after surgery.

Outcome measures: HRQOL was assessed with the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and the oesophageal cancer-specific module (EORTC QLQ-OES18). The number of removed lymph nodes in relation to HRQOL was analysed using multivariable linear regression, providing mean score differences in HRQOL scores with 95% CIs. The results were adjusted for age, comorbidity, body mass index, tumour stage, tumour histology, postoperative complications and surgeon volume.

Results: The study included 382 and 136 patients who completed the EORTC questionnaires at 6 months and 5 years following surgery, respectively. In general, HRQOL remained stable over time, with only improvements in role function and appetite loss. A larger number of removed lymph nodes did not decrease the HRQOL measure at 6 months or 5 years after surgery.

Conclusions: More extensive lymphadenectomy during oesophageal cancer surgery might not decrease patients' short-term or long-term HRQOL, but larger studies are needed to establish this potential lack of association.

INTRODUCTION

Oesophageal cancer is the sixth most common cause of cancer-related death worldwide.¹ Today, surgical resection of the oesophagus together with neoadjuvant therapy is the primary option for most patients selected for curatively intended

Strengths and limitations of this study

- It is a nationwide, population-based study with high inclusion rate of patients who have undergone curatively intended oesophageal cancer surgery.
- Limited statistical power, especially in the 5-year data, may have resulted in that moderate or weak differences between groups have remained undetected.
- The lack of baseline health-related quality of life (HRQOL) assessment has precluded adjustment for potential preoperative differences in HRQOL between groups. However, it is unlikely that any such differences would be dependent on level of lymphadenectomy.

treatment.² The prognosis for patients diagnosed with oesophageal cancer is poor, but early tumour detection substantially increases the chance of survival.³ Oesophageal cancer often spreads through the lymphatic system, and the lymph node metastasis status is the strongest prognostic factor. To ensure oncological completeness, extensive lymphadenectomy during oesophageal cancer surgery is currently recommended.^{4 5} However, recent studies indicate that extensive lymph node resection might not increase survival rate.^{6 7} A more extensive lymphadenectomy may, on the other hand, increase the surgical trauma and thus increase the risk of postoperative complications, for example, anastomotic leak, bleeding, infections, lymph leak and palsy of the laryngeal nerve. Approximately 50% of patients experience at least one postoperative complication after oesophagostomy that may require immediate intervention such as reoperation or intensive care admission.^{8 9} Surgery in itself and postoperative complications are associated with long-lasting deterioration in health-related quality of life (HRQOL),^{10–14} and increased healthcare usage.¹⁵ To optimise the surgical

treatment of oesophageal cancer, it is important to investigate if and how patients' HRQOL is influenced by extensive lymphadenectomy, especially if the survival rate is not improved by this factor. We aimed to test the hypothesis that more extensive surgical lymph node removal during oesophageal cancer surgery reduces patients' short-term and long-term HRQOL.

METHODS

Study design

This was a nationwide, population-based cohort study including 90% of all patients who underwent curatively intended oesophageal cancer surgery in Sweden during a 5-year period (2 April 2001–31 December 2005). Patients were followed up until the end of 2010, that is, up to 5 years following surgery. All participants gave informed consent.

Data collection

The procedure of the nationwide data collection has been described in detail elsewhere.^{8 16} In short, the study was based on a complete, nationwide network of Swedish hospitals and clinicians involved in the treatment of patients with oesophageal cancer.¹⁷ Data regarding patient characteristics, tumour stage, type and location, and surgical procedure and complications were prospectively collected. The cohort also includes information about patients' self-reported HRQOL up to 5 years postoperatively.

Exposure and outcome

The study exposure was the number of removed lymph nodes during oesophageal cancer surgery. The outcome was HRQOL at 6 months and 5 years after the operation, assessed by two well-validated self-administered questionnaires developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC):

1. The EORTC QLQ-C30 is a 30-item core cancer questionnaire assessing five functional dimensions of HRQOL (physical, role, cognitive, emotional and social), one global QOL scale, three symptom scales (fatigue, nausea/vomiting, pain) and six single items (appetite loss, constipation, dyspnoea, insomnia, diarrhoea and financial difficulties). The instrument is valid and reliable for HRQOL measurement in a broad range of patients with cancer.¹⁸
2. The EORTC QLQ-OES18 is an 18-item questionnaire for assessing problems specific to patients with oesophageal cancer. The questionnaire consists of four scales addressing dysphagia, eating difficulties, reflux and oesophageal pain, and six single items for choking when swallowing, coughing, speech difficulties, taste dysfunction, problems swallowing saliva and dry mouth. The questionnaire has shown good psychometric validity and is recommended when measuring HRQOL in patients with oesophageal cancer.^{19 20}

Patients rated their perceived HRQOL and disease-specific problems on a four-graded Likert-type scale, choosing between the following responses: 'not at all', 'a little', 'quite a bit' and 'very much'. One measure, global QOL, was rated on a seven-grade scale ranging from 1 (very poor) to 7 (excellent). The questionnaire responses were transformed into scores between 0 and 100 and missing items were handled as recommended in the EORTC scoring manual.²¹ In functional scales and global QOL, high scores indicate better HRQOL, whereas high scores in symptom scales and items correspond to more severe symptomatic problems. Up to three reminders were sent to the participants if no response was obtained.

Statistical analysis

The total number of lymph nodes removed was categorised into quartiles in the analysis, with the first quartile (lowest lymph node harvest) used as reference category. Mean questionnaire score differences with 95% CIs were calculated. A mean score of 10 or more was considered clinically relevant according to previous research.^{22 23} We used multivariable longitudinal linear regression to analyse the association between lymphadenectomy and HRQOL. Potential confounders included in the multivariable model were as follows: (1) age (categorised as <60, 60–75 or >75 years), (2) comorbidity (0, 1 or ≥ 2 according to the Charlson Comorbidity Index Score²⁴), (3) body mass index (normal weight <24.9; overweight 25–29.9; or obese ≥ 30), (4) tumour stage (0–I, II, III or IV), (5) tumour histology (adenocarcinoma or squamous cell carcinoma), (6) postoperative complications (0 or ≥ 1 complication) and (7) cumulative surgeon volume of oesophagectomies (0–6 or >6 operations per year²⁵). 'High volume' (>6 operations per year) and 'low volume' (0–6 operations per year) surgeons were also analysed separately, that is, in stratified analyses. For comparison of HRQOL over time in relation to extent of lymph node removal, statistical significance was analysed when the mean score differences were ≥ 10 . *p* Value <0.01 was considered as statistically significant. The statistical software SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) was used for all statistical analyses.

RESULTS

Among 616 patients who underwent curatively intended oesophageal cancer surgery during the study period, 512 patients (83%) survived the first 6 months. Among these, 382 patients (75%) responded to the 6-month questionnaires and were thus included in the present study. Out of these participants, 148 survived (25%) for 5 years, of whom 136 (92%) also completed the 5-year questionnaires. Characteristics of the included patients and non-responding patients were similar, except that non-responders were older, more often had advanced tumour stages and had more comorbidities (data not shown).

Characteristic data for included patients at 6 months are presented in [table 1](#), and for those at 5 years in [table 2](#). Most patients were males, aged between 60 and

Table 1 Characteristics of 382 patients assessed 6 months after oesophageal cancer surgery

Characteristics	Categorisation	Total cohort N (%)	Lymph nodes removed in quartiles (range)			
			I (0–8) N (%)	II (9–14) N (%)	III (15–24) N (%)	IV (24–81) N (%)
Total		382	97	101	88	96
Age	<60 years	93 (24)	21 (22)	24 (24)	21 (24)	27 (28)
	60–75 years	240 (63)	65 (67)	61 (67)	56 (64)	58 (60)
	>75 years	49 (13)	11 (11)	16 (16)	11 (12)	11 (12)
Sex	Men	311 (81)	76 (78)	82 (82)	76 (86)	77 (80)
	Women	71 (19)	21 (22)	19 (18)	12 (14)	19 (20)
Comorbidity	0	116 (53)	59 (61)	55 (54)	44 (50)	56 (58)
	1	65 (30)	19 (19)	30 (30)	23 (26)	26 (27)
	>1	38 (17)	19 (20)	16 (16)	21 (24)	14 (15)
Body mass index	<25	184 (48)	39 (40)	49 (48)	43 (49)	53 (55)
	25 to <30	120 (31)	38 (40)	30 (30)	27 (31)	25 (26)
	≥30	63 (16)	15 (15)	20 (20)	15 (17)	13 (14)
	Missing data	15 (4)	5 (5)	2 (2)	3 (3)	5 (5)
Tumour stage	0–I	50 (23)	32 (33)	14 (14)	13 (15)	20 (21)
	II	64 (29)	25 (26)	37 (37)	29 (33)	24 (25)
	III	88 (40)	35 (36)	45 (44)	36 (41)	40 (42)
	IV	17 (8)	5 (5)	5 (5)	10 (11)	12 (12)
Tumour histology	Squamous cell carcinoma	65 (30)	22 (23)	24 (24)	25 (28)	22 (23)
	Adenocarcinoma	154 (70)	75 (77)	77 (76)	72 (72)	77 (77)
Postoperative complications	0	252 (66)	62 (64)	68 (67)	55 (63)	67 (70)
	≥1	130 (34)	35 (36)	33 (33)	33 (37)	29 (30)
Surgeon volume (operations/year)	0–6	163 (43)	54 (56)	57 (57)	29 (33)	23 (24)
	>6	219 (57)	43 (44)	44 (43)	59 (67)	73 (76)

Table 2 Characteristics of 136 patients assessed 5 years after oesophageal cancer surgery

Characteristics	Categorisation	Total cohort N (%)	Lymph nodes removed in quartiles (range)			
			I (0–8) N (%)	II (9–14) N (%)	III (15–24) N (%)	IV (24–81) N (%)
Total		136	33	30	33	40
Age	<60 years	36 (26)	8 (24)	7 (23)	11 (33)	10 (25)
	60–75 years	92 (68)	23 (70)	18 (60)	21 (64)	30 (75)
	>75 years	8 (6)	2 (6)	5 (17)	1 (3)	0 (0)
Sex	Men	108 (79)	27 (82)	24 (80)	27 (82)	30 (75)
	Women	28 (21)	6 (18)	6 (20)	6 (18)	10 (25)
Comorbidity	0	75 (55)	20 (61)	14 (47)	21 (64)	20 (50)
	1	38 (28)	5 (15)	11 (37)	8 (24)	14 (35)
	>1	23 (17)	8 (24)	5 (16)	4 (12)	6 (15)
Body mass index	<25	62 (46)	12 (36)	13 (43)	15 (46)	22 (55)
	25 to <30	46 (34)	14 (43)	8 (27)	12 (36)	12 (30)
	≥30	27 (20)	7 (21)	8 (27)	6 (18)	6 (15)
	Missing data	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)
Tumour stage	0–I	64 (47)	24 (73)	13 (43)	9 (27)	18 (45)
	II	41 (30)	7 (21)	9 (30)	15 (46)	10 (25)
	III	27 (20)	2 (6)	8 (27)	8 (24)	9 (23)
	IV	4 (3)	0 (0)	0 (0)	1 (3)	3 (7)
Tumour histology	Squamous cell carcinoma	34 (25)	6 (18)	7 (23)	11 (33)	10 (25)
	Adenocarcinoma	102 (75)	27 (82)	23 (77)	22 (67)	30 (75)
Postoperative complications	0	87 (64)	21 (64)	21 (70)	20 (61)	25 (62)
	≥1	49 (36)	12 (36)	9 (30)	13 (39)	15 (38)
Surgeon volume (operations/year)	0–6	55 (40)	16 (48)	19 (63)	11 (33)	9 (23)
	>6	81 (60)	17 (52)	11 (37)	22 (67)	31 (77)

75 years and without comorbidities. The median number of removed lymph nodes was 14 (range 0–81). Patient characteristics in the four lymphadenectomy quartile groups were similar, except for more advanced tumour stages and higher surgeon volume in lymphadenectomy quartiles III and IV. Median length of survival was similarly distributed in the four quartiles.

Extent of lymph nodes removal and short-term HRQOL

There was no influence of more extensive surgical lymph node removal on HRQOL at 6-month follow-up (table 3). Global QOL, functions, and general and

oesophageal symptoms were similar between the lymphadenectomy quartiles, with no clinically significant differences in mean questionnaire scores. Data were also stratified by two categories of surgeon volume, but the results were similar in both categories (data not shown).

Extent of lymph node removal and long-term HRQOL

Long-term HRQOL showed no deterioration in patients with more extensive lymph node resection (table 4). Results remained similar when data were stratified by surgeon volume (data not shown). Global QOL, function and symptom scales did not reveal any worse mean score

Table 3 Number of lymph nodes removed (quartiles I–IV) in relation to health-related quality of life aspects in 382 patients 6 months after oesophageal cancer surgery

Questionnaire scales and items	Adjusted* questionnaire scores	Mean score differences (95% CIs)		
	I (0–8 nodes) Reference	II (9–14 nodes)	III (15–24 nodes)	IV (24–81 nodes)
EORTC QLQ-C30				
Global quality of life	50 (45 to 56)	3 (–3 to 10)	1 (–5 to 8)	6 (0 to 13)
<i>Functional scales</i>				
Physical	68 (62 to 73)	1 (–5 to 6)	0 (–6 to 6)	3 (–3 to 9)
Role	53 (45 to 61)	5 (–4 to 14)	0 (–9 to 10)	4 (–5 to 13)
Cognitive	75 (70 to 80)	6 (0 to 12)	1 (–6 to 7)	1 (–5 to 8)
Emotional	63 (58 to 69)	9 (2 to 15)	4 (–2 to 11)	4 (–3 to 10)
Social	63 (56 to 70)	8 (1 to 16)	2 (–6 to 10)	5 (–2 to 13)
<i>Symptom scales</i>				
Fatigue	53 (46 to 60)	–3 (–11 to 4)	–2 (–10 to 6)	–4 (–11 to 4)
Nausea/vomiting	26 (20 to 31)	–6 (–12 to 0)	–6 (–13 to 0)	–8 (–15 to –2)
Pain	36 (29 to 43)	–7 (–14 to 1)	3 (–5 to 11)	1 (–7 to 9)
<i>Symptom items</i>				
Appetite loss	47 (39 to 55)	1 (–8 to 11)	–2 (–12 to 7)	–5 (–15 to 4)
Constipation	19 (14 to 25)	–2 (–9 to 4)	–8 (–14 to –1)	–3 (–10 to 3)
Dyspnoea	42 (35 to 50)	0 (–8 to 9)	3 (–6 to 11)	0 (–9 to 8)
Insomnia	31 (23 to 38)	–3 (–12 to 5)	–2 (–11 to 7)	1 (–8 to 9)
Diarrhoea	33 (25 to 41)	–5 (–13 to 4)	–3 (–12 to 6)	–9 (–18 to 0)
Financial difficulties	19 (13 to 26)	2 (–5 to 9)	3 (–4 to 11)	1 (–6 to 8)
EORTC QLQ-OES18				
<i>Disease-specific symptom scales</i>				
Dysphagia	31 (24 to 38)	1 (–7 to 8)	–2 (–10 to 6)	–6 (–14 to 2)
Eating difficulties	41 (35 to 47)	–1 (–8 to 6)	0 (–7 to 8)	–4 (–11 to 3)
Reflux	25 (18 to 32)	–2 (–11 to 6)	–3 (–12 to 6)	–2 (–10 to 6)
Oesophageal pain	31 (25 to 37)	–9 (–15 to –2)	–1 (–8 to 6)	–5 (–12 to 2)
<i>Disease-specific items</i>				
Choking	22 (16 to 29)	0 (–7 to 7)	6 (–1 to 13)	–2 (–10 to 5)
Coughing	28 (21 to 36)	2 (–7 to 10)	–4 (–13 to 5)	0 (–9 to 9)
Speech difficulties	18 (12 to 23)	0 (–7 to 6)	1 (–5 to 8)	–2 (–9 to 4)
Taste problems	30 (23 to 37)	–7 (–15 to 1)	–1 (–9 to 8)	–4 (–12 to 5)
Trouble swallowing saliva	14 (8 to 21)	5 (–3 to 12)	1 (–7 to 8)	3 (–5 to 10)
Dry mouth	27 (20 to 35)	4 (–4 to 13)	2 (–7 to 11)	1 (–8 to 9)

*Adjusted for age, comorbidity, body mass index, tumour stage, tumour histology, postoperative complications and cumulative surgeon volume.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire oesophageal cancer-specific module.

Table 4 Number of lymph nodes removed (quartiles I–IV) in relation to health-related quality of life aspects in 136 patients 5 years after oesophageal cancer surgery

Questionnaire scales and items	Adjusted* questionnaire scores	Mean score differences (95% CIs)		
	I (0–8 nodes) Reference	II (9–14 nodes)	III (15–24 nodes)	IV (24–81 nodes)
EORTC QLQ-C30				
Global quality of life	59 (50 to 67)	5 (–6 to 16)	4 (–7 to 14)	0 (–11 to 10)
<i>Functional scales</i>				
Physical	74 (66 to 82)	–5 (–15 to 5)	–3 (–13 to 7)	1 (–8 to 11)
Role	64 (52 to 77)	4 (–12 to 20)	6 (–9 to 22)	9 (–6 to 24)
Cognitive	74 (65 to 82)	5 (–6 to 15)	–2 (–13 to 8)	5 (–5 to 15)
Emotional	68 (59 to 77)	9 (–2 to 21)	6 (–5 to 17)	6 (–4 to 17)
Social	74 (64 to 85)	3 (–11 to 16)	3 (–10 to 16)	2 (–10 to 14)
<i>Symptom scales</i>				
Fatigue	46 (35 to 56)	–9 (–23 to 4)	1 (–12 to 14)	–3 (–15 to 10)
Nausea/vomiting	15 (6 to 23)	–1 (–12 to 10)	2 (–9 to 13)	–1 (–11 to 9)
Pain	23 (12 to 33)	1 (–12 to 15)	7 (–6 to 20)	11 (–2 to 23)
<i>Symptom items</i>				
Appetite loss	41 (28 to 54)	–10 (–26 to 6)	–8 (–24 to 8)	–16 (–31 to –1)
Constipation	11 (2 to 19)	4 (–7 to 14)	4 (–7 to 15)	3 (–7 to 14)
Dyspnoea	39 (27 to 50)	–3 (–18 to 12)	2 (–12 to 17)	0 (–14 to 14)
Insomnia	36 (24 to 47)	–8 (–24 to 7)	–10 (–24 to 5)	0 (–15 to 14)
Diarrhoea	33 (21 to 45)	–12 (–27 to 4)	–13 (–28 to 2)	–16 (–30 to –2)
Financial difficulties	17 (7 to 26)	–3 (–15 to 10)	0 (–12 to 12)	0 (–12 to 11)
EORTC QLQ-OES18				
<i>Disease-specific symptom scales</i>				
Dysphagia	29 (19 to 40)	–4 (–18 to 9)	–4 (–17 to 10)	–7 (–19 to 6)
Eating difficulties	40 (30 to 50)	–12 (–25 to 1)	–10 (–22 to 2)	–13 (–25 to –2)
Reflux	29 (18 to 40)	0 (–14 to 15)	3 (–11 to 17)	7 (–6 to 21)
Oesophageal pain	23 (14 to 32)	3 (–9 to 14)	–1 (–12 to 11)	0 (–11 to 10)
<i>Disease-specific items</i>				
Choking	19 (9 to 29)	–3 (–16 to 9)	3 (–10 to 15)	–2 (–13 to 10)
Coughing	16 (4 to 27)	4 (–11 to 19)	8 (–6 to 23)	5 (–9 to 20)
Speech difficulties	15 (6 to 24)	–4 (–15 to 7)	0 (–11 to 11)	–5 (–15 to 6)
Taste problems	27 (15 to 38)	–13 (–28 to 1)	–7 (–21 to 7)	–6 (–20 to 7)
Trouble swallowing saliva	9 (–1 to 19)	13 (0 to 25)	12 (0 to 24)	3 (–9 to 15)
Dry mouth	23 (11 to 35)	2 (–13 to 17)	9 (–6 to 24)	–3 (–17 to 11)

*Adjusted for age, comorbidity, body mass index, tumour stage, tumour histology, postoperative complications and cumulative surgeon volume.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire oesophageal cancer-specific module.

differences with more extensive lymphadenectomy. Patients with the highest number of resected nodes (quartile IV) had rather less severe symptoms of appetite loss (mean score difference: –16, 95% CI –31 to –1), diarrhoea (mean score difference: –16, 95% CI –30 to –2) and eating difficulties (mean score difference: –13, 95% CI –25 to –2) compared with the reference group (quartile I). Trouble swallowing saliva was more often found to be a problem in patients in lymphadenectomy quartile II (mean score difference: 13, 95% CI 0 to 25) and III (mean score difference: 12, 95% CI 0 to 24). Three-year follow-up data were also analysed, but these were similar to the 5-year data and are therefore not presented.

Extent of lymph node removal and HRQOL changes between 6 months and 5 years

Most HRQOL aspects were similar between patients in the four categories of lymph node yield when analysing HRQOL changes between 6 months and 5 years of surgery (table 5). A clinically relevant and statistically significant improvement was seen in role function for patients in quartile III (mean score difference: 17, 95% CI 5 to 30) and quartile IV (mean score difference: 16, 95% CI 4 to 28). Appetite loss was clinically and statistically significantly reduced during the time period for patients in quartile IV (mean score difference: –16, 95% CI –28 to –4).

Table 5 Changes in health-related quality of life in relation to number of lymph nodes removed (quartiles I–IV) for 136 patients with data at 6 months and 5 years after oesophageal cancer surgery, presented as mean score differences (MSDs), 95% CIs and p values

Questionnaire scales and items	Health-related quality of life changes between 6 months and 5 years							
	I (0–8 nodes)		II (9–14 nodes)		III (15–24 nodes)		IV (24–81 nodes)	
	MSD (95% CI)	p Value*	MSD (95% CI)	p Value*	MSD (95% CI)	p Value*	MSD (95% CI)	p Value*
EORTC QLQ-C30								
Global quality of life	8 (–1 to 17)	–	9 (0 to 19)	–	11 (2 to 20)	0.02	2 (–7 to 10)	–
<i>Functional scales</i>								
Physical	7 (–2 to 15)	–	1 (–7 to 9)	–	4 (–4 to 12)	–	5 (–3 to 12)	–
Role	11 (–1 to 24)	0.08	10 (–3 to 24)	0.12	17 (5 to 30)	0.008	16 (4 to 28)	0.008
Cognitive	–1 (–10 to 7)	–	–3 (–12 to 6)	–	–4 (–13 to 5)	–	2 (–6 to 10)	–
Emotional	5 (–4 to 14)	–	6 (–4 to 15)	–	7 (–2 to 16)	–	8 (0 to 16)	–
Social	11 (1 to 22)	0.04	5 (–6 to 16)	–	12 (2 to 23)	0.02	8 (–2 to 18)	–
<i>Symptom scales</i>								
Fatigue	8 (–18 to 3)	–	–13 (–24 to –2)	0.02	–4 (–15 to 6)	–	–7 (–17 to 3)	–
Nausea/vomiting	–11 (–20 to –2)	0.01	–5 (–14 to 4)	–	–3 (–12 to 6)	–	–4 (–12 to 5)	–
Pain	–13 (–24 to –2)	0.02	–5 (–16 to 6)	–	–9 (–20 to 2)	–	–3 (–13 to 7)	–
<i>Symptom items</i>								
Appetite loss	–6 (–19 to 7)	–	–17 (–31 to –4)	0.01	–11 (–24 to 2)	0.08	–16 (–28 to –4)	0.009
Constipation	–9 (–18 to 0)	–	–3 (–12 to 6)	–	3 (–6 to 12)	–	–2 (–10 to 6)	–
Dyspnoea	–3 (–15 to 9)	–	–7 (–19 to 6)	–	–4 (–16 to 8)	–	–3 (–14 to 8)	–
Insomnia	5 (–7 to 17)	–	0 (–13 to 12)	–	–3 (–15 to 9)	–	4 (–7 to 15)	–
Diarrhoea	–1 (–13 to 12)	–	–7 (–20 to 5)	–	–10 (–23 to 2)	0.10	–8 (–19 to 4)	–
Financial difficulties	–3 (–13 to 7)	–	–8 (–18 to 3)	–	–6 (–16 to 4)	–	–4 (–13 to 5)	–
EORTC QLQ-OES 18								
<i>Disease-specific symptom scales</i>								
Dysphagia	–2 (–13 to 9)	–	–7 (–18 to 4)	–	–3 (–14 to 8)	–	–3 (–13 to 8)	–
Eating difficulties	–1 (–11 to 9)	–	–12 (–22 to –1)	0.03	–11 (–21 to –1)	0.03	–10 (–20 to –1)	0.03
Reflux	4 (–8 to 15)	–	6 (–5 to 18)	–	10 (–2 to 22)	0.10	13 (2 to 24)	0.02
Oesophageal pain	–9 (–18 to 1)	–	3 (–7 to 12)	–	–8 (–18 to 1)	–	–4 (–13 to 5)	–
<i>Disease-specific items</i>								
Choking	–4 (–14 to 6)	–	–7 (–17 to 4)	–	–7 (–17 to 3)	–	–3 (–12 to 6)	–
Coughing	–13 (–25 to 0)	0.04	–10 (–22 to 3)	0.12	0 (–13 to 12)	–	–7 (–18 to 4)	–
Speech difficulties	–3 (–12 to 6)	–	–7 (–16 to 3)	–	–5 (–14 to 4)	–	–5 (–14 to 3)	–
Taste problems	–3 (–15 to 9)	–	–10 (–22 to 2)	0.12	–10 (–21 to 2)	0.11	–6 (–17 to 5)	–
Trouble swallowing saliva	–6 (–16 to 5)	–	2 (–8 to 13)	–	6 (–4 to 16)	–	–6 (–15 to 4)	–
Dry mouth	–4 (–17 to 8)	–	–7 (–19 to 6)	–	3 (–10 to 15)	–	–8 (–19 to 3)	–

p Values <0.01 were considered statistically significant.

*Where mean scores differed clinically relevantly by ≥ 10 points, linear regression was used to test for statistical significance.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire oesophageal cancer-specific module.

DISCUSSION

In this study, more extensive lymph node removal during oesophageal cancer surgery did not decrease patients' short-term or long-term HRQOL. Irrespective of the extent of lymphadenectomy, few clinical improvements in HRQOL over time were seen.

However, results should be interpreted in the light of study strengths and limitations. A nationwide population-based design with high inclusion rate of patients who underwent curatively intended oesophageal cancer surgery reduces the risk of selection bias. Yet, even though follow-up rate at 6 months and 5 years was high (75% and 92%, respectively), we cannot preclude that non-participation influenced the results, since responders tended to be healthier. However, it is unlikely that non-participation was associated with the extent of lymphadenectomy, and thus selection bias should not be a major concern. The number of identified lymph nodes is a result of the lymphadenectomy per se, but the pathologists also play an important role in identifying lymph nodes. Therefore, some level of exposure misclassification is expected. Such bias is likely at random, but may lead to dilution of potential associations. However, the number of detected lymph nodes in this population-based study of all hospitals in Sweden remains a valid marker of the extent of lymphadenectomy. The use of well-validated questionnaires reduced the risk of information bias. Results were adjusted for all established prognostic factors, which counteracts confounding. However, residual confounding cannot be eliminated, for example, by surgeon volume. More experienced surgeons tend to remove more lymph nodes and they have better postoperative outcomes regarding complications and mortality.²⁶ However, stratification by surgeon volume did not change the results. The results were adjusted for several potential confounding factors, but we did not adjust for surgical technique. The reason for this is that the dominating surgical procedure in Sweden during the entire study period was the 'Ivor-Lewis technique'. Therefore, we do not believe that surgical technique was a confounder in the present study. The lack of baseline HRQOL assessment is a limitation that precludes adjustment for potential preoperative differences in HRQOL between groups. However, it is unlikely that any such differences would be dependent on level of lymphadenectomy. No power calculation was performed since the study population was defined beforehand. Limited statistical power, especially in the 5-year data, may have resulted in moderate or weak differences between groups remaining undetected.

Oesophageal cancer surgery is known to bring about long-lasting deterioration in HRQOL.¹³ The hypothesis that such deterioration is associated with more extensive lymphadenectomy was not confirmed in this study. The difference for transhiatal oesophagectomy and transthoracic oesophagectomy with more extensive lymphadenectomy have previously been evaluated in a

randomised clinical trial²⁷ and in observational research,²⁵ where no differences in HRQOL beyond 3 months of surgery were observed. These results supported by findings in this study, may suggest that factors other than the extent of lymphadenectomy are involved in patients' trajectory of recovery. Comorbidity, more advanced tumour stages and proximal tumour location are other factors that seem to reduce HRQOL.¹⁶

More extensive lymphadenectomy introduces greater surgical trauma, but if extensive lymphadenectomy does not increase survival^{6, 7} or decrease HRQOL, a discussion is needed regarding the preferred level of lymphadenectomy. A more tailored lymphadenectomy might be the optimal surgical procedure to reduce morbidity for these patients.²⁸ However, since multidirectional spread is common in patients with oesophageal cancer, it may be difficult to identify and obtain sentinel nodes.

In conclusion, this population-based cohort study indicates that a more extensive lymphadenectomy during oesophageal cancer surgery does not decrease the short-term or long-term HRQOL. There is a need for larger studies to establish the relation between extent of lymphadenectomy and long-term HRQOL.

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