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Health-related quality of life following total minimally invasive, hybrid minimally invasive or open oesophagectomy: a population-based cohort study

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Abstract

Background: Minimally invasive oesophagectomy has been shown to reduce the risk of pulmonary complications compared with open oesophagectomy, but the effects on health-related quality of life (HRQoL) and oesophageal cancer survivorship remain unclear. The aim of this study was to assess the longitudinal effects of minimally invasive compared with open oesophagectomy for cancer on HRQoL.

Methods: All patients who had surgery for oesophageal cancer in Sweden from January 2013 to April 2018 were identified. The exposure was total or hybrid minimally invasive oesophagectomy, compared with open surgery. The study outcome was HRQoL, evaluated by means of the European Organisation for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-OG25 at 1 and 2 years after surgery. Mean differences and 95 per cent confidence intervals were adjusted for confounders.

Results: Of the 246 patients recruited, 153 underwent minimally invasive oesophagectomy, of which 75 were hybrid minimally invasive and 78 were total minimally invasive procedures. After adjustment for age, sex, Charlson Co-morbidity Index score, pathological tumour stage and neoadjuvant therapy, there were no clinically and statistically significant differences in overall or disease-specific HRQoL after oesophagectomy between hybrid minimally invasive and total minimally invasive surgical technique *versus* open surgery.

Conclusion: In this population-based nationwide Swedish study, longitudinal HRQoL after minimally invasive oesophagectomy was similar to that of the open surgical approach.

Introduction

Surgical resection remains the mainstay of oesophageal cancer treatment with curative intent. During recent decades, minimally invasive oesophagectomy has shown increasing promise as the primary surgical option for oesophageal cancer, given the reduction in postoperative pulmonary complications and duration of hospital stay compared with open oesophagectomy[1]. Hybrid minimally invasive oesophagectomy (HMIO) comprises open surgery with either a laparoscopic or thoracoscopic technique. Previous studies[2–4] have established that short-term postoperative outcomes are improved after HMIO compared with open surgery, similar to the results after total minimally invasive oesophagectomy (TMIO). Different surgical strategies for oesophagogastric cancers produce similar oncological outcomes[5]. However, the use of a minimally invasive surgical technique may offer better postoperative health-related quality of life (HRQoL) up to 2 years after treatment[3,6–10]. This makes sense, as complications are known to be strongly associated with poor postoperative HRQoL both in the short and the long term[11]. However, previous studies comparing HRQoL after open and minimally invasive surgery involved hospital-based cohorts, or were RCTs with strict patient and surgeon inclusion criteria, limiting the external validity of the findings. Whether HRQoL is different after open and minimally invasive surgical techniques in a population-based setting has not been evaluated previously. Moreover, the link between potentially reduced complications and improved HRQoL has not been examined.

The aim of this study was therefore to clarify the impact of minimally invasive oesophagectomy compared with open oesophagectomy on longitudinal HRQoL in a nationwide, population-based cohort study. A further aim was to elucidate whether postoperative complications underly potential differences in HRQoL up to 2 years after treatment.

Methods

This nationwide prospective cohort study included all patients who had survived 1 year after surgical resection for oesophageal

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or gastro-oesophageal junction cancer in Sweden between 2013 and 2018. After the initial assessment, patients were followed up at 1·5 and 2 years after surgery. For the purpose of this study, the 1- and 2-year measurements were included. Eligible patients were identified through the pathology departments in all hospitals that manage oesophageal cancer in Sweden. A project coordinator recruited patients to the study and was responsible for follow-up. A research nurse visited the participating patients in their homes 1 year after surgery for collection of patient-reported outcomes (PROs). Follow-up PROs were collected using paper questionnaires and the project coordinator contacted all patients by telephone before all follow-ups.

Patient-reported outcomes

HRQoL was measured using questionnaires developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC). The 30-item core questionnaire (QLQ-C30) has nine multi-item scales measuring global quality of life, function (physical, role, cognitive, emotional and social functioning) and symptoms (fatigue, pain, nausea and vomiting), and six single items measuring general cancer symptoms (dyspnoea, appetite loss, insomnia, constipation, diarrhoea and financial impact)[12]. Oesophageal cancer-specific symptoms were measured by means of the supplementary module QLQ-OG25, which comprises six symptom scales (dysphagia, eating restriction, reflux, pain when eating, pain and discomfort, and anxiety) and ten 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). Each item on both questionnaires has a four-point Likert scale (1, not at all; 2, a little; 3, quite a bit; and 4, very much), except for the global quality-of-life scale in the QLQ-C30, which has seven response alternatives ranging from very poor to excellent[12,13].

Clinical data

Clinical details at the time of surgery were collected from medical records and included: tumour histology, tumour location, resection margin status and tumour stage. Treatment details included: surgical approach, neoadjuvant or adjuvant oncological treatment, complications and duration of hospital stay. Medical records were reviewed according to a predefined study protocol to ensure consistency and uniformity of data collection. The quality of the review was controlled with random validation by two independent researchers.

Exposures

The exposure was TMIO (thoracoscopic and laparoscopic) and HMIO (thoracoscopic/open abdomen or laparoscopic/open chest), compared with open oesophagectomy (open abdomen and chest).

Outcomes

The primary outcome was HRQoL measured by mean scores on the scales and items in the EORTC QLQ-C30 and QLQ-OG25 at 1, 1·5 and 2 years after surgery. The secondary outcome was effects of postoperative complications in the exposure groups on HRQoL. Postoperative outcomes were compiled with the purpose of investigating the association between postoperative complications and HRQoL after open oesophagectomy compared with TMIO and HMIO. All complications were classified according to the Clavien–Dindo classification for postoperative complications[14].

Surgical complications that occurred within the first 30 days after operation were considered: anastomotic leak, as assessed by CT with oral water-soluble contrast medium, with any uncertainty followed up endoscopically; conduit necrosis, defined by clinically significant ischaemia with perforation or ulcer; postoperative bleeding, analysed as a continuous variable; chylothorax, defined as pleural effusion requiring drainage for more than 7 days or requiring surgical reintervention; recurrent laryngeal nerve paralysis diagnosed by a specialized otolaryngologist; abdominal or thoracic abscess verified radiologically or surgically; clear clinical signs of wound rupture or wound infection requiring antibiotic treatment; small bowel obstruction requiring surgical intervention; and gastric perforation requiring surgical intervention.

Postoperative non-surgical complications within 30 days included: septicaemia diagnosed based on a body temperature above 38·3°C or below 36·0°C, and/or a positive blood culture; kidney failure, defined by the need for dialysis; respiratory failure, defined by the need for invasive or non-invasive ventilator treatment; liver failure, defined by progressive transient or chronic jaundice; pneumonia diagnosed by pathological chest X-ray findings and fever, cough and/or dyspnoea; pulmonary or other embolism, defined as a radiologically confirmed embolus requiring treatment; deep vein thrombosis verified radiologically and requiring treatment; and cardiovascular complications, including cardiac arrhythmias requiring medical treatment, myocardial infarction defined by clinical symptoms with ECG changes or positive enzyme test, and cerebral embolism.

Statistical analysis

All analyses were based on an *a priori* protocol and conducted by an expert biostatistician specialized in analysis of HRQoL. Longitudinal mixed-effect regression models with a time interaction term were used to calculate mean HRQoL score differences with 95 per cent confidence intervals. Clinically significant differences were based on the evidence-based guidelines for interpreting changes in scores in EORTC questionnaires[15]. If no guideline on a given item was available, a difference of 10 points was considered clinically significant[16]. Variables that could be associated with both the choice of surgical procedure (exposure) and HRQoL (primary outcome) and postoperative complications (secondary outcome), that is potential confounding factors, were prespecified and included in multivariable adjusted models: age (continuous variable), sex, Charlson Co-morbidity Index score (0, 1 or at least 2), pathological tumour stage (0–I, II or III–IV) and neoadjuvant therapy (yes or no). An additional model was created with the addition of Clavien–Dindo grade of complications. χ^2 and Fisher's exact test were used to assess the distribution of complications across surgical techniques with a 5 per cent level of significance. SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Results

In total, 246 patients were included in the study, representing an inclusion rate of 64·7 per cent of patients alive 1 year after treatment; 93 patients underwent open oesophagectomy, 75 had HMIO and 78 TMIO (*Fig. 1*). Patient characteristics are shown in *Table 1*. Open oesophagectomy was used to a greater degree in women and in patients with squamous cell carcinoma. HMIO was performed with thoracoscopy and laparotomy in 17 patients, and thoracotomy and laparoscopy in 58. The use of neoadjuvant therapy was similar across the groups and there was no significant difference in Charlson Co-morbidity Index scores. In the open oesophagectomy group, 63 per cent of patients had

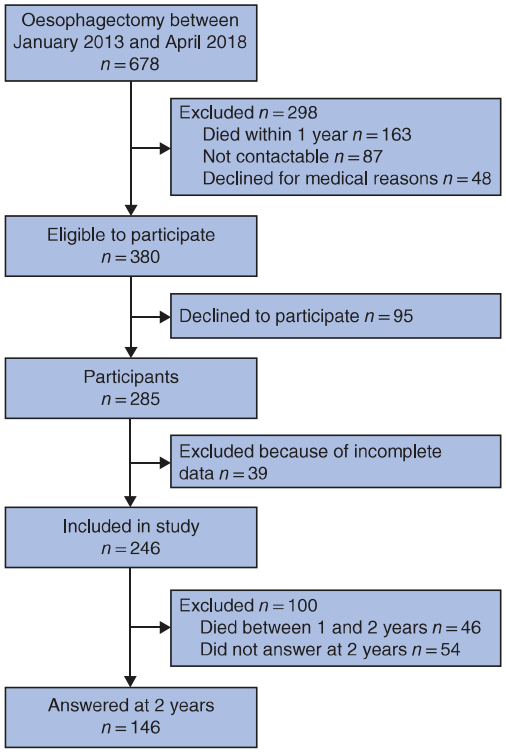

Fig. 1 Study flow chart

pathological tumour stage II–IV compared with 57 per cent in the HMIO and 79 per cent in the TMIO group.

Postoperative complications occurred in 69 per cent of patients after open oesophagectomy, 64 per cent after HMIO and 63 per cent after TMIO. The most common complication in the open oesophagectomy group was pneumonia, which affected 26 per cent, compared with 19 per cent after HMIO and 18 per cent after TMIO. The most common complications after HMIO were atrial fibrillation and pneumonia (both 19 per cent). The anastomotic leak rate was 12 per cent after open oesophagectomy and 15 per cent after HMIO; the rate was significantly higher after TMIO and was the most common complication, occurring in 27 per cent of the patients. Most leaks (over 95 per cent) were managed with a conservative approach without thoracotomy. Conduit necrosis was diagnosed in 3·2 per cent of patients after open oesophagectomy, none after HMIO and 3 per cent after TMIO. Respiratory failure rates were 19, 7 and 14 per cent respectively. After open oesophagectomy 32 per cent of patients had a complication with a Clavien–Dindo grade of IIIb or higher, compared with 21 per cent after HMIO and 27 per cent after TMIO. There was no statistically significant difference in recurrence rate or 2-year survival between the groups (*Table 2*).

Health-related quality of life after minimally invasive compared with open surgery

After adjustment for age, sex, Charlson Co-morbidity Index, pathological tumour stage and neoadjuvant therapy, there were no major differences in HRQoL between groups. The level of HRQoL was substantially decreased and patients had significant symptoms in all groups. The global quality-of-life score was 61 (95 per cent c.i. 56 to 66) 1 year after open oesophagectomy and 62 (56 to 68) at 2 years, with no clinically relevant or statistically significant differences compared with HMIO at 1 year (62, 56 to 67) or 2 years (63, 55 to 70), or TMIO at 1 year (59, 54 to 65) or 2 years (65, 57 to 73). A similar pattern was found for physical functioning scores, which were 77 (73 to 82) at 1 year and 75 (70 to 80) 2 years after open oesophagectomy. The role functioning score was 9 points higher after TMIO compared with open oesophagectomy 2 years after treatment, but this was not clinically relevant or statistically significant. Dyspnoea, pain and fatigue scores were similar in the groups (*Fig. 2a*).

All groups had a relatively high level of problems with postoperative symptoms. A clinically relevant difference was found for coughing after TMIO at 2-year follow-up; the score was 10 points lower than that after open oesophagectomy ($P = 0·098$) (*Fig. 2b*). A clinically relevant difference was also found for anxiety: patients treated with HMIO reported 10-point lower scores than those after open oesophagectomy at 2-year follow-up ($P = 0·063$). Neither of the clinically relevant differences was statistically significant.

Health-related quality of life after minimally invasive compared with open surgery in model including Clavien–Dindo grade

Additional analyses were performed in a model adjusted for Clavien–Dindo grade to evaluate the effects of severity of postoperative complications. This further adjustment did not have any clinically or statistically significant impact on the results. Data are available in *Tables S1–S4* (supporting information).

Discussion

This nationwide population-based cohort study, comparing HRQoL after minimally invasive *versus* open oesophagectomy, showed that use of either technique did not change the fact that HRQoL is decreased at 1 to 2 years after treatment. Pneumonia and respiratory failure were less common after HMIO and TMIO, but the overall frequency and severity of complications, measured by means of the Clavien–Dindo grade, did not differ between the groups, and had no mediatory effects on HRQoL. Anastomotic leaks were more common in the TMIO group. The results of the study demonstrate that oesophagectomy is associated with substantial negative effects on HRQoL and symptoms. The impairment was at a level similar to that described in previous studies[17,18].

The strengths of the study include the population-based design, with all patients who had surgery for oesophageal cancer in Sweden asked to participate, leading to a large cohort and a high participation rate. Every included patient was visited at home by a research nurse, which ensured high quality of data collection. All patients' records were reviewed according to a standardized protocol by researchers not involved in the care of the patients, restricting the potential for any reporting bias. Limitations of the study are that only patients alive 1 year after treatment were included, which limits the generalizability of the findings. There was no measurement of HRQoL before treatment, which precludes comparison of the groups at baseline. Furthermore, the analysis of complications was limited as those who had the most severe complications and died within the first postoperative year could not be included in the study. However, the aim of this study was to evaluate longitudinal HRQoL, comparing minimally invasive techniques with open oesophagectomy to increase knowledge of oesophageal cancer survivorship. Minimally invasive oesophagectomy is known to have a learning curve which have might influenced the results of the study; however, the inclusion of complications in the adjusted model did not change the results

Table 1 Patient characteristics stratified by surgical technique for oesophagectomy

	Open oesophagectomy ($n = 93$)	Hybrid minimally invasive oesophagectomy ($n = 75$)	Total minimally invasive oesophagectomy ($n = 78$)
Age (years)*	65·8 (29·9–82·0)	67·1 (46·3–83·2)	66·2 (38·2–83·7)
Sex ratio (F : M)	19 : 74	7 : 68	8 : 70
Histological tumour type			
Squamous cell carcinoma	17 (18)	9 (12)	13 (17)
Adenocarcinoma	76 (82)	66 (88)	65 (83)
Clinical tumour stage			
I	13 (14)	14 (19)	12 (15)
II	18 (19)	16 (21)	21 (27)
III–IV	21 (23)	18 (24)	38 (49)
Unknown	41 (44)	27 (36)	7 (9)
Charlson Co-morbidity Index score			
0	44 (47)	36 (48)	37 (47)
1	30 (32)	28 (37)	23 (29)
≥ 2	19 (20)	11 (15)	18 (23)
Neoadjuvant treatment			
Yes	74 (80)	62 (83)	58 (74)
No	19 (20)	13 (17)	20 (26)
Surgical approach			
Transthoracic oesophagectomy, Ivor Lewis	74 (80)	64 (85)	56 (72)
Transthoracic oesophagectomy, McKeown	6 (6)	6 (8)	15 (19)
Transhiatal oesophagectomy	0 (0)	0 (0)	2 (3)
Other oesophagectomy	11 (12)	2 (3)	0 (0)
Unknown	2 (2)	3 (4)	5 (6)
Anastomotic technique			
Stapled	62 (67)	48 (64)	67 (86)
Handsewn	29 (31)	25 (33)	9 (12)
Unknown	2 (2)	2 (3)	2 (3)
Anastomotic site			
Neck	9 (10)	9 (12)	20 (26)
Thorax	75 (81)	64 (85)	54 (69)
Abdomen	5 (5)	1 (1)	0 (0)
Unknown	4 (4)	1 (1)	4 (5)
Intraoperative blood loss (ml)†	645 (528, 762)	486 (329, 643)	244 (156, 331)
Pathological tumour stage			
0–I	34 (37)	32 (43)	16 (21)
II	28 (30)	21 (28)	33 (42)
III–IV	31 (33)	22 (29)	29 (37)

Values in parentheses are percentages unless indicated otherwise; values are *mean (range) and †mean (95 per cent c.i.).

of the analyses. A possible explanation could be that the learning curve for minimally invasive oesophagectomy decreased the benefits demonstrated in the MIRO trial[10].

Long-term survival after oesophageal cancer has substantially increased over the past few years[19]. The postoperative 90-day mortality rate in high-volume centres is now below 5 per cent, and the focus is shifting towards improving cancer survivorship and specifically postoperative functional results and HRQoL[20]. Minimally invasive oesophagectomy is increasingly being used, but approximately 50 per cent of oesophagectomies are still done with an open technique[20]. Some previous studies investigated HRQoL after minimally invasive oesophagectomy. The Dutch randomized TIME trial[3], which compared HRQoL after TMIO *versus* open oesophagectomy suggested an improved average global quality of life, and reduced pain 1 year after TMIO compared with an open procedure. However, this study had strict inclusion criteria and the population is not representative of typical patients undergoing oesophagectomy, limiting the external validity of the findings. The results of HRQoL analyses in the French MIRO[18] trial showed that HMIO was associated with a statistically significant increase in global quality of life and social functioning compared with open oesophagectomy, which was possibly an effect of the reduced complication rate in the HMIO group. Furthermore, a Chinese matched cohort study[8] that included 888 patients with oesophageal squamous cell carcinoma suggested better global HRQoL and physical function, as well as less fatigue and pain at 12 months but not later, after TMIO compared with the open technique. However, this was a single-centre study and not applicable to Western societies. A meta-analysis[21] of HRQoL outcomes from 2017 showed no difference in HRQoL at 12 months in a comparison of any minimally invasive oesophagectomy *versus* open oesophagectomy. In the present study, TMIO was not associated with worse HRQoL than open oesophagectomy on any of the functional or symptom scales and items. Similarly, there were no differences in HRQoL between HMIO and open oesophagectomy. Taken together, these results support the view that the choice between minimally invasive and open oesophagectomy does not lead to long-standing differences in patient HRQoL.

The primary outcome of the ongoing British ROMIO (Randomized Oesophagectomy: Minimally Invasive or Open) trial, which is randomizing patients to minimally invasive or open

Table 2 Postoperative complications stratified by surgical technique for oesophagectomy

	Open oesophagectomy ($n = 93$)	Hybrid minimally invasive oesophagectomy ($n = 75$)	Total minimally invasive oesophagectomy ($n = 78$)	P*
Any complication	64 (69)	48 (64)	49 (63)	0·679
Clavien–Dindo grade				0·392
I	4 (4)	2 (3)	0 (0)	
II	21 (23)	21 (28)	15 (19)	
IIIa	9 (10)	9 (12)	13 (17)	
IIIb	9 (10)	8 (11)	10 (13)	
IVa	14 (15)	4 (5)	9 (12)	
IVb	7 (8)	4 (5)	2 (3)	
Surgical complication	33 (35)	20 (27)	29 (37)	0·331
Anastomotic leak	11 (12)	11 (15)	21 (27)	0·026
Conduit necrosis	3 (3)	0 (0)	2 (3)	0·383
Postoperative bleeding	1 (1)	1 (1)	0 (0)	0·759
Chylothorax	3 (3)	3 (4)	2 (3)	0·908
Recurrent laryngeal nerve paralysis	6 (6)	3 (4)	5 (6)	0·832
Abdominal abscess	1 (1)	2 (3)	2 (3)	0·738
Thoracic abscess	9 (10)	3 (4)	5 (6)	0·358
Wound rupture	0 (0)	0 (0)	0 (0)	–
Wound infection	9 (10)	4 (5)	3 (4)	0·331
Small bowel obstruction	2 (2)	1 (1)	0 (0)	0·642
Gastric perforation	1 (1)	0 (0)	0 (0)	1·000
Non-surgical complication	43 (46)	31 (41)	33 (42)	0·790
Septicaemia	17 (18)	8 (11)	9 (12)	0·284
Kidney failure	2 (2)	2 (3)	1 (1)	0·866
Respiratory failure	18 (19)	5 (7)	11 (14)	0·060
Liver failure	0 (0)	1 (1)	0 (0)	0·305
Pneumonia	24 (26)	14 (19)	14 (18)	0·374
Pulmonary embolism	4 (4)	2 (3)	4 (5)	0·788
Other embolism	0 (0)	1 (1)	0 (0)	0·305
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	–
Myocardial infarction	1 (1)	2 (3)	1 (1)	0·691
Atrial fibrillation	14 (15)	14 (19)	9 (12)	0·468
Stroke	0 (0)	0 (0)	0 (0)	–
Recurrence within 2 years	13 (14)	20 (27)	21 (27)	0·062
Death within 2 years	14 (15)	14 (19)	18 (23)	0·407

Values in parentheses are percentages. *χ^2 or Fisher's exact test.

oesophagectomy, is fatigue, measured using the Multidimensional Fatigue Inventory 3 years after treatment. The results of the trial may clarify whether fatigue or other aspects of HRQoL or postoperative symptoms are improved by use of a minimally invasive technique.

An association between postoperative complications and reduced longitudinal HRQoL has been described previously[22,23], which prompted the analysis of HRQoL after minimally invasive *versus* open oesophagectomy in relation to complications. The reduced risk of postoperative complications after TMIO and HMIO compared with open oesophagectomy can be hypothesized to be a possible reason for improvements in HRQoL[2,4,24]. However, complication grade had no effect on the comparison between minimally invasive and open oesophagectomy in the present analysis. In previous studies[17,22,23,25] examining complications and HRQoL, the associations between medical, including pulmonary, complications and worse HRQoL became more pronounced over time, being strongest at 5 and 10 years. In the present study, most patients in the HMIO group underwent thoracotomy, which is often thought to be the reason for increased pulmonary complications after open oesophagectomy. The reduced risk of pulmonary complications after HMIO shown in a previous study[2] was confirmed in 1-year survivors of oesophagectomy in the present analysis. Increased frequency of anastomotic leak was observed in the TMIO group, which might reduce the positive effects of not having a thoracotomy, as anastomotic leaks are associated with decreased postoperative HRQoL[11].

The study showed that functional outcomes after oesophagectomy need to be improved and that the introduction of a minimally invasive surgical technique does not seem to solve this problem. Providing adequate information to patients before and during treatment, and developing specific treatments aimed at decreasing the lasting symptoms of the operation are areas that could improve future outcomes.

The results of the present study can be used to inform patients of expected HRQoL outcomes over time. HRQoL was not affected by surgical technique between 1 and 2 years after oesophagectomy, but studies with long-term follow-up should be conducted to determine whether the reduction in pulmonary complications by minimally invasive surgery translates to better overall long-term HRQoL, improved physical status and improved survivorship in patients with oesophageal cancer.

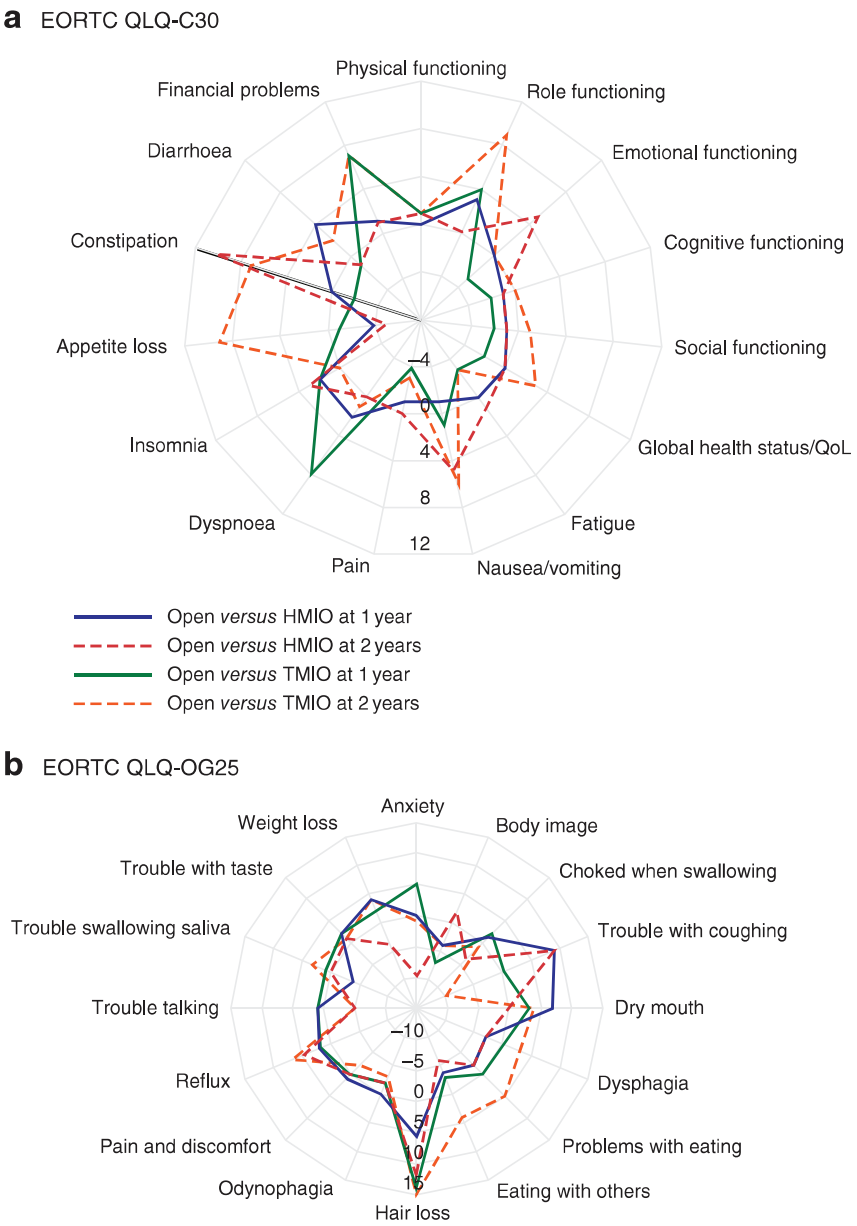

Fig. 2 Heath-related quality of life according to EORTC QLQ-C30 and QLQ-OG25 questionnaire responses stratified by surgical strategy for oesophagectomy
Spider plot showing differences in health-related quality of life (QoL) measured using a European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and b QLQ-OG25 questionnaires after open *versus* hybrid minimally invasive (HMIO) or total minimally invasive (TMIO) oesophagectomy. Estimated means and mean differences were adjusted for age, sex, Charlson Co-morbidity Index, pathological tumour category and neoadjuvant therapy.

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Disclosure: The authors declare no conflict of interest.

Supporting information

Additional supporting information can be found online in the Supporting information section at the end of the article.

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