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Lasting symptoms and long-term health-related quality of life after totally minimally invasive, hybrid and open Ivor Lewis esophagectomy

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ABSTRACT

Aim: Compared to open esophagectomy (OE), both totally minimally invasive (TMIE) and laparoscopy-assisted hybrid minimally invasive (HMIE) reduce postoperative morbidity and improve short-term health-related quality of life (HRQoL). We aimed to compare lasting symptoms and long-term HRQoL in an international population-based setting between patients who underwent Ivor Lewis TMIE, HMIE or OE.

Methods: Patients who were relapse-free at least one year after TMIE, HMIE or OE for esophageal or junctional carcinoma between January 2010 and June 2016 were included. Patients completed the LASER questionnaire to assess lasting symptoms after esophagectomy and the EORTC QLQ-C30 and QLQ-OG25 questionnaires to assess HRQoL. Primary endpoint was chest pain and secondary endpoints were pain from chest scars or abdominal scars, abdominal pain, fatigue and physical functioning. Differences in lasting symptoms and HRQoL were assessed with multivariable logistic and ANCOVA regression, respectively.

Results: A total of 362 patients were included (TMIE n = 91, HMIE n = 85, OE n = 186). Median follow-up was 3.9 years (IQR 2.8–5.4). Chest pain was reported less after TMIE compared with HMIE (adjusted OR 0.21, 95% CI 0.05–0.84), but was comparable between TMIE and OE (adjusted OR 0.41, 95% CI 0.12–1.41) and between HMIE and OE (adjusted OR 1.85, 95% CI 0.71–4.81). All secondary endpoints were comparable between TMIE, HMIE and OE. The impact of symptoms on taking medication, return to work, and performance status were comparable between groups.

Conclusion: Surgical technique seems to have little effect on lasting symptoms and long-term HRQoL after a median of four years after Ivor Lewis esophagectomy.

1. Introduction

Esophagectomy is the cornerstone of treatment for patients with esophageal cancer. One of the most common surgical approaches and the preferred approach for tumors located in the middle or distal esophagus is an Ivor Lewis esophagectomy (*i.e.* transthoracic esophagectomy with intrathoracic anastomosis). Open esophagectomy (OE), however, is associated with relatively high postoperative morbidity and mortality, lasting symptoms in two thirds of patients and decreased long-term health-related quality of life (HRQoL) [1–3]. In order to minimize postoperative morbidity and improve HRQoL, especially of transthoracic esophagectomy, minimally invasive approaches have been introduced.

Abbreviations: ORE, Operator Reliability Experiment; HCR/ORE, Human Cognitive Reliability/ Operator Reliability Experiment; OPERA, Operator Performance and Reliability Analysis; EMBRACE -APR1400 (EMpirical data-Based crew Reliability Assessment and Cognitive Error analysis), MERMOS; Méthode d'Evaluation de la Réalisation des Missions Opérateurs pour la Sûreté, HuRECA; Human Reliability Evaluator for Control Room Actions, HuREX; Human Reliability data Extraction, SACADA; Scenario Authoring, Characterization and Debriefing Application; IDHEAS-ECA, Integrated Human Event Analysis System; Event Condition Analysis, IDHEAS-G; Integrated Human Event Analysis System, General Methodology.

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Randomized trials have suggested that compared to OE, totally minimally invasive esophagectomy (TMIE) leads to less pulmonary complications and shorter hospital stay and hybrid minimally invasive esophagectomy (HMIE) leads to less pulmonary and less total major complications [4,5]. Also, both surgical techniques may lead to better short-term HRQoL than OE [6,7]. With Ivor Lewis TMIE, however, a thoracoscopic intrathoracic anastomosis is required, which is known to be technically challenging and can lead to severe anastomotic leakage [8]. While no randomized studies have compared TMIE and HMIE, a meta-analysis has suggested that TMIE may be associated with less wound infections and pneumonia whereas HMIE may lead to less anastomotic leakage [9].

However, the effect of these different minimally invasive techniques on lasting symptoms and long-term HRQoL remains unclear. In the present study, we aimed to assess whether Ivor Lewis TMIE is associated with reduced long-term pain and better long-term physical functioning than HMIE and OE. Moreover, we aimed to assess the impact of surgical complications on lasting symptoms and HRQoL as well as the impact of lasting symptoms on work and functional ability.

2. Methods

2.1. Study design and patients

The present study is a side-study of the multicenter cross-sectional LASER study, of which details have been published previously [2]. Briefly, patients with carcinoma of the esophagus or gastroesophageal junction (Siewert type I and II) who underwent esophagectomy with curative intent between January 1, 2010 and June 30, 2016 were included from 15 European centers. Patients were eligible if they were relapse-free at least 12 months after completion of curative esophagectomy, adjuvant treatment, or salvage esophagectomy for failed endoscopic or definitive oncological treatment, and if they had no ongoing surgical complications besides an anastomotic stricture or diaphragmatic hernia. Assessment of relapse-free status varied, but most centers performed a CT scan after 1 year of follow-up. Patients who still required non-oral nutrition were excluded. For the present study, we only included patients who underwent an Ivor Lewis esophagectomy. Hence, patients with a cervical anastomosis were excluded. The institutional review board at each participating center had approved the study protocol.

2.2. Exposure

The exposure within this study was surgical technique: TMIE, HMIE or OE. Ivor Lewis esophagectomy consists of an abdominal phase (mobilization of the stomach) and a right-sided thoracic phase (resection of the esophagus and intrathoracic anastomosis). During TMIE, both phases are performed minimally invasively, requiring a thoracoscopic intrathoracic anastomosis. For the present study, the procedure was considered a HMIE if the abdominal phase was performed minimally invasively and the thoracic phase was open. During OE, both phases are performed in an open fashion.

2.3. Data collection

Data from the LASER study were used [2]. In this study, eligible

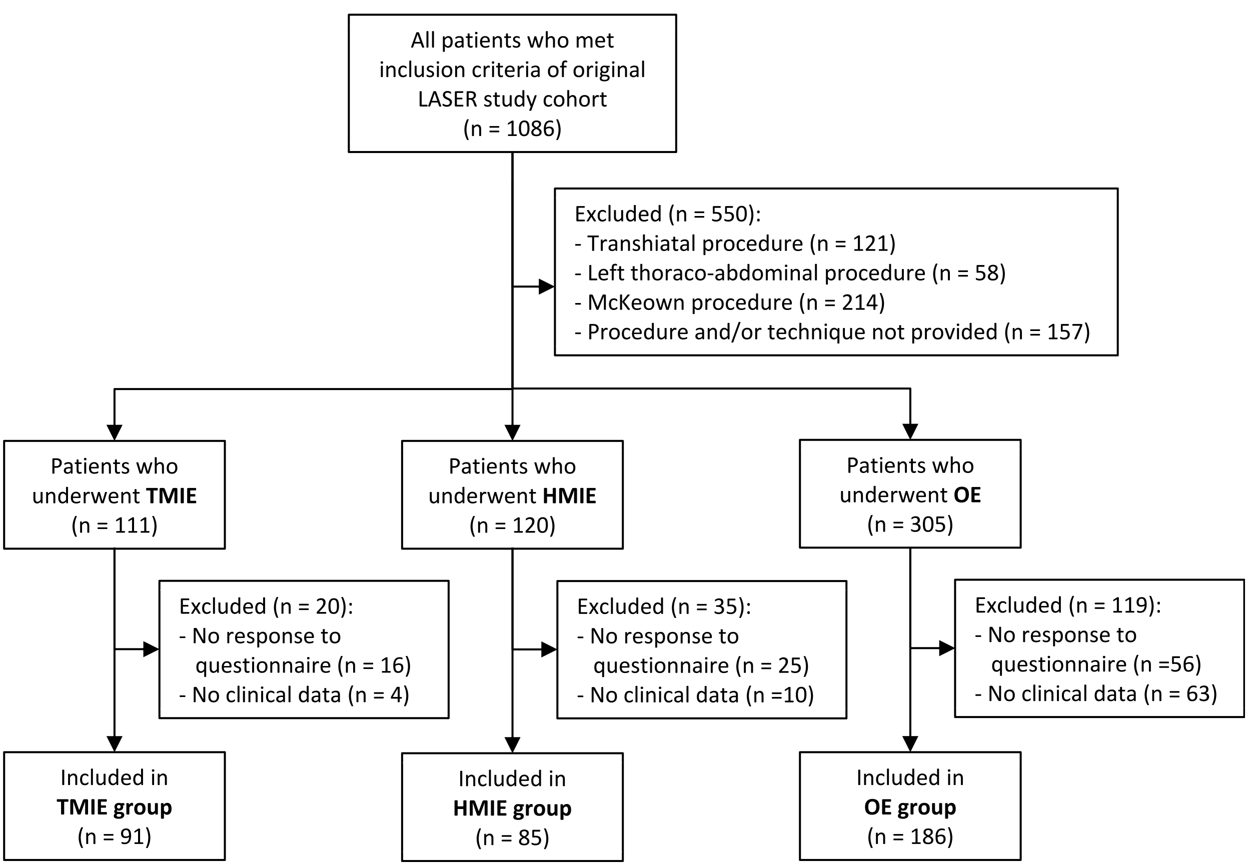

Fig. 1. Flow chart of included from the LASER study into the present side-study.

Table 1
Demographic and clinical characteristics of patients who underwent totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), or open Ivor Lewis esophagectomy (OE).

Characteristic	Total	TMIE	HMIE	OE
Total number	362	91	85	186
Age, median (IQR)	65 (52–78)	65 (51–79)	65 (51–79)	64 (52–76)
BMI				
at surgery, median (IQR)	26.4 (20.8–31.9)	24.4 (19.5–29.4)	26.6 (20.8–32.3)	26.6 (21.6–31.6)
at questionnaire, median (IQR)	23.9 (19.5–28.3)	23.3 (18.6–28.1)	23.6 (17.7–29.6)	24.2 (20.4–28.0)
Sex, n (%)				
Female	60 (17)	17 (19)	13 (15)	30 (16)
Male	302 (83)	74 (81)	72 (85)	156 (84)
Neoadjuvant therapy, n (%)				
Yes	290 (80)	73 (80)	66 (78)	151 (81)
No	72 (20)	18 (20)	19 (22)	35 (19)
Adjuvant therapy, n (%)				
Yes	75 (21)	4 (4)	19 (22)	52 (28)
No	248 (69)	54 (59)	63 (74)	131 (70)
Missing	39 (11)	33 (36)	3 (4)	3 (2)
Pathological TNM stage, n (%)[a]				
Stage 0	65 (18)	19 (21)	19 (22)	27 (15)
Stage I	109 (30)	22 (24)	32 (38)	55 (30)
Stage II	98 (27)	9 (10)	24 (28)	65 (35)
Stage III-IV	90 (25)	41 (45)	10 (12)	39 (21)
Complications, n (%)				
No complications	176 (49)	55 (60)	42 (49)	79 (42)
Clavien-Dindo 1-2	102 (28)	17 (19)	20 (24)	65 (35)
Clavien-Dindo $\geq$ 3	78 (22)	18 (20)	20 (24)	40 (22)
Missing	6 (2)	1 (1)	3 (4)	2 (1)
Type of anastomosis, n (%)				
End to end	87 (24)	0 (0)	27 (32)	60 (32)
End to side	246 (68)	64 (70)	56 (66)	126 (68)
Side to side	29 (8)	27 (30)	2 (2)	0 (0)
Anastomosis construction, n (%)				
Hand-sewn	113 (31)	1 (1)	22 (26)	90 (48)
Linear stapler	47 (13)	28 (31)	10 (12)	9 (5)
Circular stapler	202 (56)	62 (68)	53 (62)	87 (47)

IQR: interquartile range, BMI: body mass index, TNM: tumor-node-metastasis.
[a] according to the Union for International Cancer Control TNM staging manual, 7th edition.

patients were identified from institutional databases and were invited at the outpatient clinic, by telephone or by letter to participate in the study. At least a year after surgery, patients were asked to once complete three questionnaires: the LASER questionnaire, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-OG25 [2,10,11]. Questionnaires could be completed either web-based or paper-based.

2.4. Measurements

Lasting symptoms over the past 6 months of long-term survivors after esophagectomy were assessed by the self-completed LASER questionnaire. This questionnaire has been developed by a cooperation of European upper GI-surgeons and patient panels in the United Kingdom, Sweden, Italy and France. The LASER questionnaire contains 28 symptoms, of which the frequency is scored on a 5-point scale (never, rarely, weekly, daily or multiple times per day) and impact on quality of life (QoL) on a 3-point scale (none, some, substantial). These scores are combined into a composite score from 0 to 5: 0, no symptom present; 1, present but no impact on QoL; 2, rarely or weekly and some impact on QoL; 3, daily or multiple times per day and some impact on QoL; 4, rarely or weekly and substantial impact on QoL; 5, daily or multiple times per day and substantial impact on QoL.

Cancer-related HRQoL was assessed by the validated EORTC QLQ-C30 questionnaire, which consists of five functional scales, three symptom scales and one global HRQoL scale [10]. Esophageal cancer-specific HRQoL was assessed by the validated EORTC QLQ-OG25 questionnaire, which consists of six multi-item symptom scales and ten single items [11]. Scores are measured on a 4-point Likert scale: 1, not at all; 2, a little; 3, quite a bit; 4, very much. Only global HRQoL is measured on a 7-point scale ranging from ‘poor’ to ‘excellent’.

Predefined primary endpoint was chest pain (LASER). Predefined secondary endpoints were: pain from chest scars (LASER), abdominal pain (LASER), pain from abdominal scars (LASER), fatigue (QLQ-C30) and physical functioning (QLQ-C30). Prior to the analysis, these endpoints were defined by consensus discussion with experienced esophageal surgeons, based on clinical relevance and hypothesized association with the surgical techniques.

2.5. Statistical analysis

Patients were stratified into three groups according to surgical technique: TMIE, HMIE or OE. Follow-up time was calculated from date of surgery until date of completion of the questionnaire.

The composite LASER symptom scores were dichotomized into low (0, 1, 2) and high (3, 4, 5). Differences between the three surgical techniques were calculated by using multivariable logistic regression and were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). In case a primary or secondary endpoint was reported with only low or only high scores and thus no aOR could be estimated, association was tested using Fisher's exact test.

Scores from QLQ-C30 and QLQ-OG25 were linearly transformed to a 0–100 score according to the EORTC manual [12]. Differences between groups were calculated by using multivariable ANCOVA regression and were expressed as adjusted mean scores differences (aMD) with 95% CIs. For interpretation of QLQ-C30 scores, medium

Table 2
Adjusted odds ratios for LASER symptom scores of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE).

	TMIE vs. HMIE	TMIE vs. OE	HMIE vs. OE
	aOR (95% CI)*	aOR (95% CI)*	aOR (95% CI)*
Chest pain†	**0.21 (0.05–0.84)**§	0.41 (0.12–1.41)	1.85 (0.71–4.81)
Abdominal pain‡	0.73 (0.28–1.94)	0.75 (0.33–1.69)	1.06 (0.48–2.31)
Pain from chest scars‡	0.47 (0.09–2.52)	0.45 (0.11–1.88)	0.95 (0.28–3.29)
Pain from abdominal scars‡	N/A [a]	N/A [a]	1.38 (0.11–17.87)
Difficulty getting food down	0.68 (0.25–1.84)	1.02 (0.42–2.47)	1.51 (0.67–3.41)
Difficulty getting liquids down	0.57 (0.12–2.67)	0.68 (0.17–2.72)	1.28 (0.41–4.01)
Regurgitation of food	**0.35 (0.13–0.94)**§	0.68 (0.28–1.68)	1.91 (0.90–4.06)
Nausea	0.87 (030–2.54)	1.11 (0.45–2.77)	1.22 (0.49–3.05)
Vomiting	0.69 (0.21–2.32)	3.37 (0.97–11.72)	**4.69 (1.41–15.63)**§
Early feeling of fullness after eating	1.47 (0.71–3.02)	0.99 (0.55–1.77)	0.68 (0.37–1.26)
Heart palpitation after eating	2.20 (0.48–10.14)	1.25 (0.43–3.70)	0.56 (0.15–2.13)
Sweating after eating	0.51 (0.08–3.17)	0.34 (0.08–1.44)	0.63 (0.16–2.44)
Dizziness after eating	0.21 (0.02–2.16)	0.18 (0.02–1.46)	0.79 (0.23–2.66)
Bloating or cramping after eating	1.28 (0.45–3.64)	1.00(0.42–2.35)	1.03 (0.44–2.41)
Loose bowel motions/diarrhea after eating	0.52 (0.16–1.66)	**0.33 (0.13–0.86)**§	0.63 (0.27–1.45)
Heartburn/acid or bile regurgitation	0.71 (0.31–1.62)	0.80 (0.39–1.62)	1.12 (0.57–2.18)
Waking up because of choking sensation	0.78 (0.18–3.31)	0.77 (0.22–2.69)	1.09 (0.36–3.32)
Persistent cough	1.01 (0.42–2.45)	1.28 (0.59–2.77)	1.22 (0.58–2.57)
Stools that float and are difficult to flush	N/A [a]	N/A [a]	1.15 (0.36–3.64)
Diarrhea unrelated to eating	0.28 (0.06–1.34)	0.76 (0.17–3.36)	2.60 (0.77–8.80)
Lack of appetite	0.29 (0.07–1.17)	0.33 (0.09–1.21)	1.08 (0.46–2.54)
Tiredness	0.66 (0.33–1.34)	0.89 (0.49–1.62)	1.31 (0.74–2.33)
Low mood	0.27 (0.06–1.11)	0.28 (0.08–1.01)	0.97 (0.40–2.35)
Reduced energy/activity tolerance	0.88 (0.44–1.77)	0.83 (0.46–1.50)	0.92 (0.51–1.64)
Voice problems	0.80 (0.29–2.17)	1.51 (0.59–3.87)	1.84 (0.75–4.49)
Polyneuropathy	0.39 (0.13–1.13)	0.60 (0.23–1.54)	1.54 (0.70–3.38)
Dental problems	N/A [a]	N/A [a]	2.28 (0.76–6.85)
Hiccups	1.29 (0.39–4.27)	2.79 (0.85–9.15)	2.13 (0.66–6.92)

aOR: adjusted odds ratio, CI: confidence interval.
* Adjusted for age, sex, pathological TNM stage and neoadjuvant therapy.
† Predefined primary endpoint.
‡ Predefined secondary endpoints.
§ Statistically significantly different odds ratios.
a aOR could not be not estimated since the symptom was reported with only low or only high composite LASER scores in of the two groups.

or large mean score differences according to the evidence-based guidelines were considered clinically relevant [13]. For the QLQ-OG25, for which no evidence-based cut-offs are available, a difference of 10 points or more was considered medium or large and thus clinically relevant [14].

All multivariable regression models were adjusted for confounding factors, including age (continuous), sex (male or female), pathological stage (0-I, II, or III-IV; according to the Union for International Cancer Control TNM staging manual, 7th edition) and neoadjuvant therapy (yes or no). To investigate the impact of surgical complications on LASER scores and HRQoL, the same multivariable regression models were fitted but also adjusted for occurrence of surgical complications (yes or no).

Statistical analyses were performed by an experienced biostatistician with expertise in HRQoL analyses (A.J.).

3. Results

3.1. Patients

In total, 91 patients were included in the TMIE group, 85 patients in the HMIE group, and 186 in the OE group. A flowchart of patients included in the study stratified by group is shown in Fig. 1. Median follow-up time was 3.1 years (IQR 2.7–4.0) in the TMIE group, 3.2 years (IQR 2.5–5.3) in the HMIE group, and 4.8 years (IQR 3.4–6.0) in the OE group. Demographic and clinical characteristics are summarized in Table 1. Age, BMI, sex and the proportion of patients undergoing neoadjuvant therapy were comparable between groups. The proportion of patients with pathological stage III-IV was higher in the TMIE group than in the other two groups. Postoperative complications occurred most frequently in the OE group but the proportion of patients having complications of Clavien-Dindo score ≥3 was comparable between the groups.

3.2. Primary endpoint

Patients who underwent TMIE had a lower composite chest pain score than patients who underwent HMIE (aOR 0.21, 95% CI 0.05–0.84) (Table 2). No statistically significant difference in chest pain was observed between patients who underwent TMIE and OE (aOR 0.41, 95% CI 0.12–1.41) nor between patients who underwent HMIE and OE (aOR 1.85, 95% CI 0.71–4.81) (Table 2). After adjustment for surgical complications, the association between chest pain and TMIE versus HMIE remained statistically significant (aOR 0.19, 95% CI 0.05–0.80) (Supplementary Table 1).

3.3. Secondary endpoints

Pain from chest scars was comparable between TMIE and HMIE (aOR 0.47, 95% CI 0.09–2.52), TMIE and OE (aOR 0.45, 95% CI 0.11–1.88) and HMIE and OE (aOR 0.95, 95% CI 0.28–3.29) (Table 2). Abdominal pain was also comparable between TMIE and HMIE (aOR 0.73, 95% CI 0.28–1.94), TMIE and OE (aOR 0.75, 95% CI 0.33–1.69) and HMIE and OE (aOR 1.06, 95% CI 0.48–2.31) (Table 2). Pain from abdominal scars was comparable between HMIE and OE (aOR 1.38, 95% CI 0.11–17.87) (Table 2). Since none of the patients in the TMIE group reported pain from abdominal scars with a high score, the odds ratios could not be estimated for TMIE vs. HMIE and

Table 3
Adjusted mean health related quality of life (HRQoL) scores and mean difference from the EORTC QLQ-C30 and QLQ-OG25 questionnaires of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE).

	TMIE	HMIE	OE	TMIE vs. HMIE	TMIE vs. OE	HMIE vs. OE
	Mean score (95% CI)	Mean score (95% CI)	Mean score (95% CI)	aMD (95% CI)[*]	aMD (95% CI)[*]	aMD (95% CI)[*]
QLQ-C30						
Global HRQoL	73 (68–78)	70 (65–75)	67 (63–71)	4 (-2–10)	**6 (1–12)**[§]	3 (-3–8)
Functional status						
Physical Functioning[‡]	81 (77–86)	79 (75–84)	81 (77–84)	2 (-4–7)	1 (-4–5)	-1 (-6–3)
Role Functioning	87 (81–93)	80 (74–86)	83 (78–88)	7 (-1–14)	4 (-3–10)	−3 (-9–3)
Emotional Functioning	85 (80–91)	79 (73–84)	79 (74–83)	7 (0–14)	**7 (1–13)**[§]	0 (-6–6)
Cognitive Functioning	88 (83–93)	83 (78–88)	82 (78–86)	5 (-2–11)	5 (0–11)	1 (-4–6)
Social Functioning	82 (76–88)	80 (74–86)	79 (74–84)	2 (-5–10)	3 (-3–10)	1 (-5–7)
Symptom scales						
Fatigue[‡]	30 (24–36)	35 (29–41)	34 (29–38)	−5 (-12–3)	−3 (-10–3)	1 (-5–8)
Nausea/Vomiting	16 (11–20)	19 (14–23)	14 (11–18)	−3 (-8–3)	1 (-3–6)	4 (-1–9)
Pain	17 (11–22)	19 (13–25)	20 (15–24)	−2 (-9–4)	−3 (-9–3)	−1 (-6–5)
Dyspnea	21 (14–27)	24 (17–31)	25 (19–30)	−3 (-11–5)	−4 (-11–3)	−1 (-8–6)
Insomnia	25 (18–32)	30 (23–37)	27 (21–32)	−5 (-14–3)	−2 (-9–6)	3 (-4–11)
Appetite loss	19 (13–25)	22 (15–29)	21 (15–26)	−3 (-11–5)	−2 (-9–5)	1 (-5–8)
Constipation	15 (10–21)	19 (14–24)	15 (11–19)	−3 (-10–3)	1 (-5–6)	4 (-1–9)
Diarrhea	16 (11–22)	22 (16–28)	21 (17–26)	−5 (-13–2)	−5 (-11–1)	0 (-6–7)
Body image	87 (81–93)	83 (77–89)	84 (79–89)	5 (-3–12)	3 (-3–10)	−1 (-8–5)
QLQ-OG25						
Symptom scales						
Dysphagia	10 (7–14)	15 (11–19)	8 (5–11)	−4 (-9–0)	3 (-1–7)	**7 (3–11)**[§]
Problems with eating	26 (21–31)	30 (24–35)	25 (21–30)	−4 (-11–3)	1 (-5–7)	5 (-1–10)
Reflux	30 (23–36)	35 (29–42)	33 (28–39)	−6 (-14–3)	−4 (-11–4)	2 (-5–9)
Odynophagia	12 (8–17)	20 (15–24)	16 (13–20)	**−7 (-13–2)**[§]	−4 (-9–1)	3 (-2–8)
Pain and discomfort	20 (15–25)	24 (18–29)	26 (22–30)	−4 (-10–3)	−6 (-12–0)	−2 (-8–3)
Anxiety	27 (20–33)	36 (29–43)	31 (25–36)	**−9 (-18–1)**[§]	−4 (-11–3)	5 (-2–13)
Eating with others	11 (5–16)	12 (6–17)	8 (4–12)	−1 (-8–5)	3 (-3–8)	4 (-2–10)
Dry mouth	21 (14–28)	24 (17–31)	23 (18–29)	−3 (-12–6)	−2 (-10–5)	1 (-7–8)
Trouble with taste	15 (9–21)	18 (11–24)	13 (8–18)	−3 (-11–5)	2 (-5–9)	5 (-2–11)
Trouble swallowing saliva	8 (4–11)	3 (0–7)	5 (2–8)	4 (0–9)	3 (-1–7)	−1 (-5–2)
Choked when swallowing	14 (10–19)	12 (8–17)	11 (8–15)	2 (-4–8)	3 (-2–8)	1 (-4–6)
Trouble with coughing	34 (27–41)	27 (20–35)	29 (23–34)	7 (-2–16)	5 (-2–13)	−1 (-9–6)
Trouble talking scale	10 (5–15)	9 (4–14)	9 (5–12)	1 (-5–7)	1 (-4–6)	0 (-5–6)
Weight loss scale	17 (10–24)	21 (14–28)	18 (13–24)	−4 (-13–5)	−1 (-8–7)	3 (-4–10)
Hair loss scale	28 (24–31)	25 (22–29)	27 (24–29)	2 (-2–7)	1 (-3–5)	−1 (-5–2)

aMD: adjusted mean score difference, CI: confidence interval.
[*] Adjusted for age, sex, pathological TNM stage and neoadjuvant therapy. Because the values are rounded, the MDs may not exactly match the difference between the mean scores.
[‡] Predefined secondary endpoints.
[§] Statistically significant difference, but not clinically relevant difference in mean scores.

TMIE vs. OE. Association tests showed no difference between TMIE vs. HMIE ($p = 0.48$) and TMIE and OE ($p = 1.00$). Unadjusted LASER questionnaire responses of the primary and secondary endpoints are reported in Supplementary Table 2.

Fatigue levels were neither statistically nor clinically significantly different between HMIE and TMIE (aMD −5, 95% CI -12 to +3), HMIE and OE (aMD +1, 95% CI -5 to +8), and TMIE and OE (aMD −3, 95% CI -10 to +3) (Table 3). Also, physical functioning levels were neither statistically nor clinically significantly different between HMIE and TMIE (aMD +2, 95% CI -4 to +7), HMIE and OE (aMD −1, 95% CI -6 to +3), and TMIE and OE (aMD 1, 95% CI -4 to +5) (Table 3).

3.4. Other symptom and HRQoL scores

Other LASER symptom scores and HRQoL scores are reported in Tables 2 and 3. Scores adjusted for surgical complications are reported in Supplementary Tables 1 and 3

3.5. Impact of symptoms

In the TMIE group, 17 of 91 patients (19%) reported to have sought medical treatment for their symptoms, while in the HMIE group 26 of 85 patients (31%) and in the OE group 67 of 186 (36%) did (Table 4). After TMIE, HMIE and OE, the proportions of patients taking pain killers (15% vs. 13% vs. 19% resp., $p = 0.56$) and taking proton pump inhibitors were comparable (79% vs. 87% vs. 82% resp., $p = 0.45$).

Of those who worked before their diagnosis with esophageal cancer, the proportion of patients who had returned to work was comparable between the three groups ($p = 0.85$). Only 32% in the TMIE group, 21% in the HMIE group and 28% in the OE group reported to have returned to work with the same activities as before. The functional ability of patients was also comparable between the three groups ($p = 0.48$), with 36% in the TMIE group, 41% in the HMIE group and 44% in the OE group being fully active without restrictions.

4. Discussion

Although a difference in chest pain was found between TMIE and HMIE, no such difference was found between TMIE and OE. Pain from chest scars, abdominal pain and pain from abdominal scars were all comparable between patients who underwent TMIE, HMIE or OE, suggesting little effect of surgical technique on long-term chest pain. None of the HRQoL scores, including fatigue and physical functioning, were reported with a clinically relevant difference between TMIE, HMIE and OE. The impact of symptoms on

Table 4
Personal impact of symptoms of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE).

	Total	TMIE	HMIE	OE	p-value
Total number	362	91	85	186	
Sought treatment for symptoms, n (%)					
Yes	110 (30)	17 (19)	26 (31)	67 (36)	0.07
No	108 (30)	30 (33)	25 (29)	53 (28)	
Missing	144 (40)	44 (48)	34 (40)	66 (35)	
Taking PPI for symptoms, n (%)					
Yes	299 (83)	72 (79)	74 (87)	153 (82)	0.45
No	61 (17)	18 (20)	11 (13)	32 (17)	
Missing	2 (1)	1 (1)	0 (0)	1 (1)	
Taking pain killers for symptoms, n (%)					
Yes	60 (17)	14 (15)	11 (13)	35 (19)	0.56
No	287 (79)	70 (77)	69 (81)	148 (80)	
Missing	15 (4)	7 (8)	5 (6)	3 (2)	
Returned to work (if worked before), n (%)					
Yes - same work activities as before	58 (28)	14 (32)	10 (21)	34 (28)	0.85
Yes - but with some limitations/reduction in activities	50 (24)	8 (18)	13 (27)	29 (24)	
No, I have not returned to work because of my symptoms	24 (11)	4 (9)	7 (15)	13 (11)	
Now retired	75 (36)	16 (36)	16 (33)	43 (35)	
Missing	3 (1)	2 (5)	2 (4)	3 (2)	
Functional ability in past 6 months, n (%)					
0 - Fully active able to carry on all pre-disease performance without restriction	150 (41)	33 (36)	35 (41)	82 (44)	0.48
1 - Restricted in physically strenuous activity but ambulatory and able to carry out light work	176 (49)	47 (52)	39 (46)	90 (48)	
2 - Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours	26 (7)	8 (9)	6 (7)	12 (6)	
3 - Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	5 (1)	1 (1)	3 (4)	1 (1)	
4 - Cannot carry out any self-care. Totally confined to bed or chair.	0 (0)	0 (0)	0 (0)	0 (0)	
Missing	5 (1)	2 (2)	2 (2)	1 (1)	

medical treatment, on the ability to return to work and functional ability was also comparable between the groups.

TMIE and HMIE have been compared to OE in the respective randomized TIME trial and MIRO trial, both showing less postoperative complications after minimally invasive surgery with comparable oncological outcomes [4]. In the TIME trial, patients had less pain and better global HRQoL at six weeks after TMIE, which persisted up to one year [5]. Physical functioning was also better at 6 weeks and 1 year, but with limited clinical relevance. In the MIRO trial, both HMIE and OE negatively affected short-term HRQoL, including physical functioning, fatigue and pain [15]. Three years after surgery, however, all HRQoL domains of both techniques had restored to comparable preoperative levels [16]. In the present study, pain (QLQ-C30 and QLQ-OG25), physical functioning, fatigue and global HRQoL were all comparable after TMIE, HMIE and OE, which is in line with the results of the MIRO trial. The differences between the TIME trial and the present study can best be explained by the fact that the questionnaires in our study were taken after a median follow-up of 3.9 years after surgery. Hence, differences in HRQoL scores that were observed in the TIME trial after one year may have been eased off in the present study.

A meta-analysis of nine studies showed that patients who underwent minimally invasive transthoracic esophagectomy had better short-term physical functioning, fatigue, pain and global HRQoL than patients who underwent open transthoracic esophagectomy [6]. These differences were no longer present at 6 months and 1 year after surgery, which is in line with our findings. Within this meta-analysis, no difference was made between HMIE or TMIE nor between Ivor Lewis, McKeown or Oringer esophagectomy. In a recent Swedish national population-based study, HRQoL was compared at one and two years after surgery between TMIE, HMIE and OE [7]. Although no differences in any of the cancer-related or tumor-specific HRQoL domains were observed, no difference was made between Ivor Lewis esophacetomy and other surgical approaches. In the present study, some HRQoL scores were statistically significantly different. None of these differences, however, were clinically relevant as prespecified in our methods. The present study hence shows that in a cohort of only patients who underwent Ivor Lewis esophagectomy, long-term HRQoL is comparable between TMIE, HMIE and OE. Prior to the start of the study, we assumed that some differences in HRQoL could be explained by a difference in surgical complications, as pulmonary complications and anastomotic leakage occur with different incidences after TMIE, HMIE and OE. However, no clinically relevant differences were observed and therefore such a relationship could not be evaluated.

Besides HRQoL, we focused on lasting symptoms. The only significant difference in the predefined endpoints was a lower LASER score for chest pain after TMIE than after HMIE. After adjusting for surgical complications, the strength of the associations between surgical technique and chest pain did not decrease, showing that complications did not explain this symptom. From a clinical perspective, the difference in chest pain could be explained by a smaller incision and less retraction of the ribs during thoracoscopy, both reducing direct and indirect surgical trauma to the intercostal nerve or to the muscle and fascia compared to thoracotomy [17]. Even though it would be expected, no such difference in chest pain was reported between TMIE and OE. This may be explained by a difference in managing patients' expectations prior to open surgery compared to minimally invasive surgery, leading to other expectations about the severity of chest pain. As a consequence, the impact of the patients' perception on chest pain may have decreased after OE, resulting in comparably reported chest pain between TMIE and OE. While the median follow-up times in the TMIE group and HMIE group were shorter than in the OE group, we do not expect chest pain to have changed substantially from 3.1 to 4.8 years. This is supported by previous literature, showing only a slight decrease in post-thoracotomy pain in this period [18]. Moreover, we did not find a difference in pain reported in the QLQ-C30 questionnaire, which makes the difference in chest pain between HMIE and TMIE being caused by a type I error another plausible explanation. Some other differences in lasting symptoms were reported, but similar to chest pain, these differences were reported between only two groups. Therefore, management of expectations and type I errors seem more likely to explain these differences than the abdominal or thoracic phase being minimally invasive or open. In summary, although a difference in chest pain was observed between TMIE and HMIE, the clinical relevance of this difference and the other few differences between groups seem to be limited. Evidently, the impact of these lasting symptoms on medical treatment, the ability to return to work and functional ability was also comparable between TMIE, HMIE and OE.

The present study had several strengths. As a side-study of the LASER study, we used an international multicenter cohort with a high participation rate (81%), guaranteeing cross-cultural validity of our findings. We only included patients who underwent Ivor Lewis esophagectomy to ensure a clear comparison of minimally invasive techniques for this approach. Also, studies assessing many HRQoL outcomes are prone to type I errors due to multiple testing. Since each surgical technique was compared with two other techniques in the present study, more reliable information on the impact of a minimally invasive abdominal or thoracic phase could be obtained. This reduced the risk of falsely assuming that a type I error is true.

Several limitations should also be mentioned. By using composite scores on a scale from 0 to 5, the LASER questionnaire was designed to capture smaller differences in symptom frequency and impact on QoL. For the present study, however, this scale has been dichotomized, which may have led to the loss of more delicate information. If linear transformation would have been performed, smaller differences would potentially have been captured. Since linear transformation of the LASER questionnaire has not yet been validated, we chose to dichotomize the scores to generate more robust outcomes. Comparable to the LASER study, other limitations were the cross-sectional design which does not allow for assessment of effects over time and the fact that patients were asked to report symptoms that occurred in the past six months, potentially leading to recall bias. Conversions were not registered but were included in the original group as an intention-to-treat analysis.

5. Conclusions

The present study suggests that surgical technique has little effect on lasting symptoms and long-term HRQoL in patients who underwent Ivor Lewis esophagectomy and are alive and relapse-free after a median of four years after surgery. Although some differences were observed in lasting symptoms or HRQoL scores, the clinical relevance of these differences seems limited. These findings can be used to specifically inform patients about expected outcome after surgery. Whether HMIE should be preferred over TMIE or vice versa, may be determined from prospective direct comparisons such as the ongoing randomized ROMIO trial [19].

CRediT authorship contribution statement

Ben M. Eyck: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Fredrik Klevebro:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Berend J. van der Wilk:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Asif Johar:** Methodology, Data curation, Formal analysis, Writing – review & editing. **Bas P.L. Wijnhoven:** Conceptualization, Writing – review & editing. **J. Jan B. van Lanschot:** Conceptualization, Writing – review & editing. **Pernilla Lagergren:** Conceptualization, Writing – review & editing. **Sheraz R. Markar:** Conceptualization, Writing – review & editing, Supervision. **Sjoerd M. Lagarde:** Conceptualization, Writing – review & editing, Supervision.

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Appendix A. Supplementary data

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