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Surgical complications after minimally invasive oesophagectomy compared to open oesophagectomy for oesophageal cancer: A population-based, nationwide study in Finland

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ABSTRACT

Introduction: Evidence on the safety of minimally invasive oesophagectomy (MIO) compared to open oesophagectomy (OO) in nationwide practice is lacking. The aim of this study was to compare surgical complications after MIO and OO in a nationwide, population-based, unselected cohort.
Materials and methods: Descriptive statistics were used to report complications and complication categories defined by the Oesophagectomy Complications Consensus Group, major complications, reoperations and 90-day mortality in all patients undergoing MIO and OO in Finland during 2007–2016. Main outcomes were compared using logistic regression, adjusting for confounding.
Results: Out of 699 patients, 295 (42 %) underwent MIO and 404 (58 %) underwent OO. Rates of anastomotic leakage (10 % vs 14 %, OR 0.47 (0.25–0.89)), intrathoracic abscesses (3 % vs 9 %, OR 0.13 (0.05–0.46)), major complications (35 % vs 47 %, OR 0.39 (0.25–0.60)) and reoperations (18 % vs 26 %, OR 0.43 (0.26–0.73)) were lower with MIO. Rates of pneumonia (16 % vs 27 %, OR 0.62 (0.38–1.03)), intra-abdominal abscesses (0.7 % vs 3.0 %, OR 0.20 (0.04–1.13)) and 90-day mortality (3.1 % vs 6.7 %, HR 0.48 (0.18–1.26)) were lower with MIO, but non-significant after adjustment. Pulmonary complications (36 % vs 46 %, OR 0.63 (0.41–0.96)) and infectious complications (11 % vs 22 %, OR 0.41 (0.23–0.73)) were less common with MIO, while rates of cardiac, gastrointestinal, urologic, thromboembolic, and neurologic complications were similar.
Conclusion: This study suggests a significant reduction in various surgical complications in patients undergoing MIO compared to OO and that implementing MIO into nationwide practice can be done safely.

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1. Introduction

Oesophageal cancer is the 6th most common cause of cancer death worldwide [1]. The golden standard of care is multimodality treatment including oesophagectomy, which is prone to surgical complications [2]. Minimally invasive oesophagectomy (MIO) has been gaining popularity in the recent years, opposed to open oesophagectomy (OO), after the landmark TIME trial showed marked improvements in short-term outcomes after MIO [3]. MIO has later been suggested to associate with better long-term survival [4,5] and health-related quality of life [6] compared to OO.

Studies monitoring the wider application of MIO have raised concerns regarding its safety in recent years. In the TIME trial MIO resulted in less pulmonary infections, pain and intraoperative blood loss, while a Dutch nationwide study suggested increased anastomotic leaks and reinterventions without reduction in pulmonary morbidity after MIO [7]. Further analysis comparing the TIME trial and national practice in the Netherlands reported increased total complications, pulmonary complications, reoperations and length of hospital stay after MIO [8]. The International Esodata Study Group found MIO reducing pneumonia with simultaneous increases in anastomotic leakage in a recent large-scale multicenter study [9]. On the other hand, two recent trials showed that hybrid oesophagectomy and robot-assisted MIO result in less complications compared to OO [10,11]. Taken together, the evidence from clinical trials and the few national studies differ greatly. Therefore, further national studies on complications comparing MIO and OO are required.

The aim of this population-based, nationwide study was to examine the occurrence of surgical complications in patients undergoing MIO, compared to OO.

2. Methods

2.1. Study design

This study was a nationwide, population-based, retrospective cohort study, based on the Finnish National Esophago-Gastric Cancer Cohort (FINEGO) including all 12,500 patients who underwent surgical resection of oesophageal or gastric cancer in Finland during 1987–2016 [12]. Patients included in FINEGO were identified from the Finnish Cancer Registry and the Finnish Patient Registry. Their concurrent use yields a near 100 % completeness in recognition of patients [13]. In addition, several other Finnish national registries provided basic patient information such as age, sex and year of diagnosis and treatment. Detailed clinical variables such as comorbidity, tumor histology, tumor stage, neoadjuvant treatment status, surgical technique, anastomosis location and resection radicality were retrieved from patient records from all treating hospitals in Finland by expert upper gastrointestinal and thoracic surgeons. All unique surgical complications were retrieved from patient records and classified according to the Oesophagectomy Complications Consensus Group (ECCG) definitions and the Clavien-Dindo (CD) classification [14,15]. All data accrual from patient records was performed using pre-defined online forms. For the purpose of the current study, patients operated with oesophagectomy for oesophageal cancer from the year MIO was used yearly until the end of the data collection period were considered, resulting in a study period from 2007 to 2016. Patients with missing patient records, palliative resections and upper oesophageal tumors were excluded. The study was approved by the ethical committee in Northern Ostrobothnia and the governmental agencies and hospital districts involved in the study. The requirement for individual consent was waived by the Finnish Institute for Health and Welfare.

2.2. Exposure

The exposure was minimally invasive oesophagectomy, compared to open oesophagectomy.

2.3. Outcome

The main outcomes of interest were those most likely to be affected by surgical approach, namely pneumonia, anastomotic leak, intra-abdominal and intrathoracic abscesses, delayed conduit emptying and ileus. Secondary outcomes were major complications, reoperations, 90-day mortality and rates of complications and complication categories defined by ECCG.

2.4. Statistical analysis

Frequencies and percentages were calculated for major surgical complications (CD grade IIIa or higher), reoperations, 90-day mortality, all specific complications according to the ECCG framework and for complication categories defined by ECCG (pulmonary, cardiac, gastrointestinal, urologic, thromboembolic, neurological, infectious, wound/diaphragm and other) < 90 days of surgery for patients undergoing MIO and OO.

A multivariable logistic regression model comparing MIO to OO provided odds ratios (OR) with 95 % confidence intervals (CI) for major surgical complications, reoperations, anastomotic leak, pneumonia, intra-abdominal abscess, intrathoracic abscess, delayed conduit emptying, ileus and the complication categories defined by ECCG, <90 days of surgery. The model was adjusted for relevant confounders: year of surgery (continuous), age (continuous), sex (male, female), tumor stage (0-I, II, III, IV according to the 8th edition AJCC/UICC staging of cancers of the oesophagus and oesophagogastric junction [16]), comorbidity (CCI 0, 1, 2, 3 or more according to the Charlson Comorbidity Index [17]), histology (adenocarcinoma, squamous cell carcinoma or other), anastomosis location (neck, thorax), neoadjuvant treatment status (yes, no) and center oesophagectomy volume (tertiles). Center oesophagectomy volume was calculated as a 4-year moving average of annual oesophagectomies, divided into tertiles.

Multivariable Cox regression provided a hazard ratio (HR) for 90-day mortality in MIO compared to OO, adjusted for the same confounders as the multivariable logistic regression model.

To further examine MIO, frequencies and percentages were calculated for the same outcomes for patients undergoing totally minimally invasive oesophagectomy (tMIO) and hybrid oesophagectomy.

3. Results

A total of 725 cancer patients treated with oesophagectomy were identified in FINEGO from January 1st, 2007, through December 31st, 2016. Seven of these patients were excluded due to missing patient records, 5 due to palliative intent oesophagectomy and 14 with upper oesophageal tumors, resulting in a total of 699 patients undergoing oesophagectomy for oesophageal cancer being included in the current study. Of these, 295 (42 %) underwent MIO in six hospitals and 404 (58 %) underwent OO in eleven hospitals. 68 % of MIOs were performed in higher volume centers (highest tertile), compared to 16 % of OOs. Further, 238 (81 %) of the 295 MIOs were totally minimally invasive oesophagectomies (tMIO), and 57 (19 %) were performed as hybrid oesophagectomies. Patient characteristics were similar in both groups: the majority were men, had stage III tumors, no comorbidity, adenocarcinoma histology and radical resection. However, those undergoing MIO had a greater proportion of intrathoracic anastomoses (92 % vs 61 %) and neoadjuvant treatment (73 % vs 47 %), compared to OO (Table 1).

3.1. Complications and short-term outcomes in MIO vs OO

The rates of anastomotic leakage (10 % MIO vs 14 % OO, OR 0.47 (0.25–0.89)) and intrathoracic abscesses (3 % MIO vs 9 % OO, OR 0.13

Table 1
Patient- and tumor characteristics of patients undergoing minimally invasive or open oesophagectomy for oesophageal cancer in Finland in 2007–2016.

	MIO	OO	All patients
	n (%)	n (%)	n (%)
Total	295 (100.0)	404 (100.0)	699 (100.0)
Year of surgery			
Median (IQR)	2014 (2011–2015)	2011 (2009–2013)	2012 (2010–2015)
Age			
Median (IQR)	65 [59–71]	64 [58–70]	64 [58–71]
Sex			
Male	225 (76.3)	317 (78.5)	542 (73.5)
Tumor stage			
0	18 (6.1)	19 (4.7)	37 (5.3)
I	86 (29.2)	104 (25.7)	190 (27.2)
II	46 (15.6)	66 (16.3)	112 (16.0)
III	107 (36.3)	155 (38.4)	262 (37.5)
IV	25 (8.5)	46 (11.4)	71 (10.2)
Not applicable	10 (3.4)	14 (3.5)	24 (3.4)
Missing	3 (1.0)	0 (0.0)	3 (0.4)
CCI			
0	156 (52.9)	217 (53.7)	373 (53.4)
1	83 (28.1)	117 (29.0)	200 (28.6)
2	37 (12.5)	47 (11.6)	84 (12.0)
≥3	19 (6.4)	23 (5.7)	42 (6.0)
Histology			
Adenocarcinoma	235 (79.7)	291 (72.0)	526 (75.3)
Squamous cell carcinoma	50 (16.9)	99 (24.5)	149 (21.3)
Other	10 (3.4)	14 (3.5)	24 (3.4)
Anastomosis location			
Neck	23 (7.8)	156 (38.6)	179 (25.6)
Thorax	272 (92.2)	247 (61.1)	519 (74.2)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
Resection radicality			
R0	276 (93.6)	358 (88.6)	634 (90.7)
R1	16 (5.4)	30 (7.4)	46 (6.6)
R2	3 (1.0)	16 (4.0)	19 (2.7)
Neoadjuvant treatment			
Yes	214 (72.5)	190 (47.0)	404 (57.8)
No	79 (26.8)	212 (52.5)	291 (41.6)
Missing	2 (0.7)	2 (0.5)	4 (0.6)
Center volume			
Lowest tertile	27 (9.2)	109 (47.0)	217 (31.0)
Middle tertile	67 (22.7)	151 (37.4)	218 (31.2)
Highest tertile	201 (68.1)	63 (15.6)	264 (37.8)

MIO, minimally invasive oesophagectomy; OO, open oesophagectomy; IQR, interquartile range; CCI, Charlson comorbidity index.

(0.05–0.36)) were lower with MIO. Pneumonia (16 % MIO vs 27 % OO, OR 0.62 (0.38–1.03)) and intra-abdominal abscesses (0.7 % MIO vs 3.0 % OO, OR 0.20 (0.04–1.13)) were less common with MIO, but non-significant after adjusting for confounding. There were no significant differences in the occurrences of delayed conduit emptying or ileus (Table 2, Table 3).

The risk of suffering a major complication was lower in patients undergoing MIO (35 % MIO vs 47 % OO, OR 0.39 (0.25–0.60)). Reoperations were performed in 18 % of MIOs, compared to 26 % in OO (OR 0.43 (0.26–0.73)). 90-day mortality was 3.1 % in patients undergoing MIO and 6.7 % in patients undergoing OO (HR 0.48, 0.18–1.26). (Table 2, Table 3).

3.2. Complication categories in MIO vs OO

The rates of pulmonary complications (36 % MIO vs 46 % OO, OR 0.63 (0.41–0.96)), infectious complications (11 % MIO vs 22 % OO, OR 0.41 (0.23–0.73)) and other complications (10 % MIO vs 19 % OO, OR 0.30 (0.16–0.56)) were lower with MIO. The minor differences in cardiac (17 % MIO vs 16 % OO), gastrointestinal (22 % MIO vs 24 % OO), urologic (3 % MIO vs 4 % OO), thromboembolic (5 % MIO vs 4 % OO), neurologic (10 % MIO vs 13 % OO) and wound/diaphragm

Table 2
Incidence of surgical complications, reoperations and 90-day mortality in patients undergoing minimally invasive or open oesophagectomy for oesophageal cancer.

	MIO	OO
	n (%)	n (%)
Complications defined by ECCG		
Pulmonary	107 (36.3)	184 (45.5)
Pneumonia	47 (15.9)	108 (26.7)
Pleural effusion requiring additional drainage procedure	54 (18.3)	99 (24.5)
Pneumothorax requiring treatment	10 (3.4)	13 (3.2)
Atelectasis mucous plugging requiring bronchoscopy	22 (7.5)	26 (6.4)
Respiratory failure requiring reintubation	18 (6.1)	36 (8.9)
Acute aspiration	13 (4.4)	12 (3.0)
Acute respiratory distress syndrome	6 (2.0)	15 (3.7)
Tracheobronchial injury	1 (0.3)	1 (0.2)
Chest tube maintenance for air leak for >10 d postoperatively	1 (0.3)	5 (1.2)
Cardiac	50 (16.9)	66 (16.3)
Cardiac arrest requiring CPR	5 (1.7)	1 (0.2)
Myocardial infarction	0 (0.0)	3 (0.7)
Dysrhythmia atrial requiring treatment	45 (15.3)	58 (14.4)
Dysrhythmia ventricular requiring treatment	4 (1.4)	0 (0.0)
Congestive heart failure requiring treatment	0 (0.0)	12 (3.0)
Pericarditis requiring treatment	0 (0.0)	0 (0.0)
Gastrointestinal	64 (21.7)	97 (24.0)
Anastomotic leak	29 (9.8)	55 (13.5)
Type 1	8 (2.7)	3 (0.7)
Type 2	16 (5.4)	22 (5.4)
Type 3	5 (1.7)	30 (7.4)
Conduit necrosis	7 (2.3)	16 (4.0)
Type 1	3 (1.0)	4 (1.0)
Type 2	1 (0.3)	0 (0.0)
Type 3	3 (1.0)	12 (3.0)
Ileus defined as small bowel dysfunction preventing or delaying enteral feeding	5 (1.7)	6 (1.5)
Small bowel obstruction	1 (0.3)	0 (0.0)
Feeding J-tube complication	8 (2.7)	9 (2.2)
Pyloromyotomy/pyloroplasty complication	1 (0.3)	7 (1.7)
Clostridium difficile infection	2 (0.7)	7 (1.7)
Gastrointestinal bleeding requiring intervention or transfusion	5 (1.7)	6 (1.5)
Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 d postoperatively	3 (1.0)	8 (2.0)
Pancreatitis	0 (0.0)	1 (0.2)
Pancreatic fistula	0 (0.0)	2 (0.5)
Liver dysfunction	0 (0.0)	1 (0.2)
Biliary leakage	0 (0.0)	2 (0.5)
Urologic	8 (2.7)	16 (4.0)
Acute renal insufficiency (defined as doubling of baseline creatinine)	4 (1.4)	11 (2.7)
Acute renal failure requiring dialysis	1 (0.3)	2 (0.5)
Urinary tract infection	4 (1.4)	2 (0.5)
Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter	0 (0.0)	3 (0.7)
Thromboembolic	15 (5.1)	16 (4.0)
Deep venous thrombosis	2 (0.7)	1 (0.2)
Pulmonary embolus	13 (4.4)	13 (3.2)
Stroke (CVA)	1 (0.3)	3 (0.7)
Peripheral thrombophlebitis	1 (0.3)	0 (0.0)
Neurologic	30 (10.2)	54 (13.4)
Recurrent nerve injury	9 (3.0)	34 (8.4)
Type 1	8 (2.7)	33 (8.2)
Type 2	1 (0.3)	0 (0.0)
Type 3	0 (0.0)	1 (0.2)
Other neurologic injury	8 (2.7)	5 (1.2)
Acute delirium	15 (5.1)	17 (4.2)
Delirium due to alcohol withdrawal	0 (0.0)	0 (0.0)
Infectious	32 (10.8)	89 (22.0)
Wound infection requiring opening wound or antibiotics	2 (0.7)	22 (5.4)
Central IV-line infection requiring removal or antibiotics	1 (0.3)	6 (1.5)
Intra-abdominal abscess	2 (0.7)	12 (3.0)
Intrathoracic abscess	8 (2.7)	35 (8.7)

(*continued on next page*)

Table 2 (*continued*)

	MIO	OO
	n (%)	n (%)
Sepsis defined as positive blood culture	5 (1.7)	23 (5.7)
Other infections requiring antibiotics	20 (6.8)	18 (4.5)
Wound/Diaphragm	2 (0.7)	17 (4.2)
Thoracic wound dehiscence	1 (0.3)	5 (1.2)
Abdominal wall wound dehiscence	1 (0.3)	12 (3.0)
Acute abdominal wall hernia	0 (0.0)	1 (0.2)
Acute diaphragmatic hernia	0 (0.0)	0 (0.0)
Other	29 (9.8)	78 (19.3)
Chyle leak	15 (5.2)	23 (5.7)
Type 1	2 (0.7)	3 (0.7)
Type 2	7 (2.4)	12 (3.0)
Type 3	6 (2.0)	8 (2.0)
Reoperation for other reasons than bleeding, anastomotic leak or conduit necrosis	15 (5.1)	56 (13.9)
Multiple organ dysfunction syndrome	0 (0.0)	6 (1.5)
Major complications	103 (34.9)	191 (47.3)
Reoperations	52 (17.6)	105 (26.0)
90-day mortality	9 (3.1)	27 (6.7)

MIO, minimally invasive oesophagectomy; OO, open oesophagectomy; ECCG, Oesophagectomy Complications Consensus Group; CPR, cardiopulmonary resuscitation; NG, nasogastric; CVA, cerebrovascular accident; IV; intravenous.

Table 3
Multivariable logistic regression model comparing surgical complications, reoperations and 90-day mortality in patients undergoing minimally invasive or open oesophagectomy for oesophageal cancer.

	MIO	OO
	OR (95 % CI)[a]	OR (95 % CI)[a]
Individual complications		
Pneumonia	0.62 (0.38–1.03)	1.00 (reference)
Anastomotic leak	**0.47 (0.25–0.89)**	1.00 (reference)
Intra-abdominal abscess	0.20 (0.04–1.13)	1.00 (reference)
Intrathoracic abscess	**0.13 (0.05–0.36)**	1.00 (reference)
Delayed conduit emptying	2.25 (0.40–12.54)	1.00 (reference)
Ileus	1.62 (0.34–7.76)	1.00 (reference)
Complication categories		
Pulmonary	**0.63 (0.41–0.96)**	1.00 (reference)
Cardiac	0.77 (0.44–1.34)	1.00 (reference)
Gastrointestinal	0.77 (0.47–1.26)	1.00 (reference)
Urologic	0.59 (0.18–2.00)	1.00 (reference)
Thromboembolic	1.19 (0.44–3.26)	1.00 (reference)
Neurological	0.95 (0.49–1.82)	1.00 (reference)
Infectious	**0.41 (0.23–0.73)**	1.00 (reference)
Wound/Diaphragm	0.19 (0.03–1.12)	1.00 (reference)
Other	**0.30 (0.16–0.56)**	1.00 (reference)
Major surgical complication	**0.39 (0.25–0.60)**	1.00 (reference)
Risk of reoperation	**0.43 (0.26–0.73)**	1.00 (reference)
	HR (95 % CI)[a]	**HR (95 % CI)[a]**
90-day mortality	0.48 (0.18–1.26)	1.00 (reference)

MIO, minimally invasive oesophagectomy; OO, open oesophagectomy; OR, odds ratio; HR, hazard ratio; CI, confidence interval.
Statistically significant ORs in **bold** font.
[a] Adjusted for year of surgery, age, sex, tumor stage, comorbidity, histology, anastomosis location and neoadjuvant treatment status.

complications (0.7 % MIO vs 4.2 % OO) were non-significant after adjustment (Table 2, Table 3).

3.3. Other complications in MIO vs OO

Other complications less frequent with MIO were pleural effusion requiring additional drainage (18 % MIO vs 25 % OO), type 1 recurrent nerve injury (3 % MIO vs 8 % OO), wound infection (1 % MIO vs 5 % OO), sepsis (2 % MIO vs 6 % OO), wound dehiscence (0.3 % MIO vs 1.2 % OO for thoracic, 0.3 % MIO vs 3 % OO for abdominal wall). Reoperations for other reasons than bleeding, leak or conduit necrosis were less common with MIO (5 % MIO vs 14 % OO). MIO did not increase the rate of any specific complications (Table 2).

3.4. Complications in tMIO vs hybrid oesophagectomy

Rates of pneumonia, intra-abdominal and intrathoracic abscesses and ileus were similar with hybrid and tMIO. Type III anastomotic leakage (0.4 % tMIO vs 7 % hybrid) was less common with tMIO. Total leakage rates were 9.8 % for tMIO and 10.5 % for hybrid. Conduit emptying was delayed in 3 patients undergoing hybrid oesophagectomy (5.3 %) and in 0 patients undergoing tMIO. Rates of major complications (34 % tMIO vs 39 % hybrid) and reoperations (16 % tMIO vs 23 % hybrid) were lower with tMIO than the hybrid procedure. 90-day mortality was 3.4 % in tMIO and 1.8 % in hybrid oesophagectomy. Reoperations for other reasons than bleeding, leak or conduit necrosis (3 % tMIO vs 12 % hybrid) were less common with tMIO than hybrid, while rates of pleural effusion requiring additional drainage, recurrent nerve injury and wound dehiscence were similar. Gastrointestinal complications (20 % tMIO vs 28 % hybrid) were less common and cardiac complications (19 % tMIO vs 11 % hybrid) and atrial dysrhythmia (17 % tMIO vs 9 % hybrid) more common with tMIO compared to hybrid. There were no significant differences in other complication categories (Supplementary Table 1).

4. Discussion

The present study suggests a decreased risk of major complications, reoperations, anastomotic leakage and intrathoracic abscesses in patients undergoing MIO, compared to OO in a nationwide setting. The rates of pneumonia and 90-day mortality were lower with MIO, although non-significant after adjustment. In complication categories defined by ECCG, pulmonary complications and infectious complications were decreased with MIO. No significant increase in any specific complications or complication categories was detected. To the authors' knowledge, this is the first nationwide study comparing MIO to OO in all surgical complications included in the ECCG framework, with complications recorded following ECCG definitions.

The main strengths of this study are its population-based design and the highly complete FINEGO-cohort, reducing selection bias and providing sample sizes that allowed sufficient statistical power. The main weakness in this study is its retrospective design. Regardless of the adjustments for confounders it might still be that patients undergoing MIO were patients of lower surgical risk. The surgical strategy selected for each patient was dictated mostly by surgeon preference, making it probable that at least the earliest patients undergoing MIO might have been of lower operative risk. However, the patient groups were nearly identical in terms of characteristics, excluding neoadjuvant treatment. Neoadjuvant treatment became more widespread in Finland at the same time as MIO was implemented [18]. MIO was more frequently used towards the end of the study period, resulting in a more frequent use of neoadjuvant treatment in the MIO group. In addition to neoadjuvant treatment, other aspects of care outside of surgical technique were constantly evolving during the study period, possibly introducing some bias into the comparison. These effects were mitigated by adjusting the regression model with neoadjuvant treatment status and year of surgery. Some factors that could not be adjusted for, potentially affecting the outcomes in this study, include center-specific differences in practice and perioperative care [18]. Surgeon volume for mitigation of bias from surgeon-specific proficiency could not be adjusted for due to the retrospective design, as many surgeons received training abroad and reliable numbers on performed operations were not available. Oesophagectomies were formally centralized during the study period, with twelve hospitals conducting oesophagectomy and eight of them having more than 10 procedures during the study period. MIO was performed in six hospitals, and more often in higher volume hospitals than OO. However,

this trend was influenced by the overall increase in center-specific volumes over time, as both oesophageal cancer incidence and oesophagectomy rates increased. MIO was not solely performed in higher volume centers, but rather more frequently towards the end of the study period where overall center volumes were higher. Analyses were adjusted for center volume to mitigate said bias. In addition, the majority of MIOs included in the study were performed during learning phases of individual surgeons which should increase the risk of complications, and rather bias the estimates towards favoring OO in the analysis. Lastly, there may be unknown confounders which could not be taken into account in the analysis.

In the present study, pulmonary complications were reduced, and the incidence of pneumonia was lower with MIO, however the difference in pneumonia did not reach statistical significance after adjusting for confounding. A lower risk of pneumonia with MIO has been shown in the original TIME-trial, along with other RCTs and recent meta-analyses on randomized studies [3,10,11,19,20]. Previous nationwide reports have had results contrary to the present study: Markar et al. found a significant increase in pneumonia with MIO in a Dutch nationwide study [8], while Seesing et al. reported MIO not reducing pulmonary morbidity, not assessing for pneumonia separately [7]. MIO was also associated with a lower rate of anastomotic leakage in this study. More specifically, there seemed to be less type III anastomotic leakage in patients with MIO compared to OO. Part of this is likely due to the shift in leakage management towards conservative and endoscopic strategies instead of surgery during the study period, but no increase in type II or I leakage was seen either. The larger proportion of intrathoracic anastomoses in the MIO group may also explain some of the lower incidence of anastomotic leaks (as well as recurrent nerve injury) with MIO [21,22]. Speculatively, less coughing associated with MIO could reduce stress on the thoracic anastomosis. The IESG as well as Seesing et al. found leakage rates significantly increasing with MIO in wider applications, strongly associating the problem to the long proficiency-gain period and the high overall skill level required [7,9]. Such effects were not seen in the present study, and no prospective studies have reported higher risks of leakage with the minimally invasive approach. Recent meta-analyses have not reported increased leakage rates either [19,20,23]. In addition, intrathoracic abscesses were reduced in patients undergoing MIO, which could be associated to the lesser incidence of anastomotic leakage and pneumonia, as these complications often are intertwined.

90-day mortality in patients undergoing MIO was lower, however it was not statistically significant after adjustment, partly due to the low number of deaths in both groups resulting in low statistical power. Mortality-benefits have been reported in previous studies by Markar et al., however in prospective studies this evidence is lacking. Reoperations and major complications were, however, significantly less common with MIO in the present study. Conversely, Markar et al. reported increased reoperations and major complications with MIO, highlighting the complexity of the technique. Major complications were also increased in the TIME-trial. Other RCTs have shown results more in line with our study, reporting lower rates of major complications with hybrid oesophagectomy compared to OO, and lower rates of overall surgery related complications with robot-assisted MIO compared to OO [10,11]. The lower surgical trauma and smaller incisions, magnified view, less pain, better cough function and less atelectasis provided by MIO could be the technique-specific reasons contributing to the better performance of MIO in these outcomes.

The better performance of MIO compared to OO demonstrated in this study is contrary to previous nationwide reports. In the Netherlands, the increased rate of pneumonia and anastomotic leakage in patients undergoing MIO raised some concerns internationally. The study by Markar et al. highlights the lack of external validity of the TIME-trial, which is often the case with clinical trials investigating complex surgical interventions. The surgeons selected for the trial were expert surgeons beyond their learning curves, centers were high-volume expert centers and patient selection was favorable for complex high-risk surgery. In addition, a surgical quality assurance program was in place. This inarguably excludes a significant part of real-world cases, and renders generalization to day-to-day practice questionable. As randomized evidence on MIO, lacking external validity, supports the technique itself as superior in short-term outcomes, the question of safety in wider applications relies largely on how closely the trial conditions can be replicated. In nationwide practice, this would mainly focus on surgeon proficiency, as selection criteria are inevitably broader and lower volume centers are included. The present study has comparable control for confounding, an unselected population-based design and same outcome definitions as the study by Markar et al., so comparisons are feasible, and the majority of the difference in results likely does not result from difference in study design or confounding. It could therefore be argued that the driving reason for the great discrepancy between the results from Finland and the Netherlands might be the management of surgeons' proficiency-gain periods. Furthermore, a Japanese study with a large national cohort found MIO safe in practice [24]. As MIO was implemented in a large scale and an aggressive time frame in the Netherlands, reasons contributing to the difference in outcomes might include a slower, more gradual implementation and differences in training and collaboration of surgeons. Unfortunately, as both the present study and the study by Markar et al. lacked assessment of surgeon-volumes, more robust evidence on the effect of surgeon proficiency on safety in national practice remains lacking.

Recent meta-analyses have tried to provide evidence on the feasibility of MIO. Meta-analyses on randomized studies [19,20] have shown benefits on short-term outcomes with MIO compared to OO, however they still run into the same problem with the lack of generalizability to day-to-day practice due to the strict criteria in the studies chosen for the meta-analyses. Meta-analyses including observational studies [23] are susceptible to selection bias since there are only a few nationwide reports in existence with population data to be included, and the majority are single- or multicenter reports, which are effectively convenience samples from the population perspective. Therefore, the present study is among the best evidence regarding the safety of MIO in national practice.

The results of this study are encouraging that the implementation of MIO and its subsequent use in national practice can be conducted in a safe manner. This study also reports national incidences of all surgical complications related to totally minimally invasive, hybrid and open oesophagectomy for cancer, facilitating decision-making for the medical professionals involved in the care of oesophageal cancer patients. With evidence suggesting long-term benefits of MIO [4,5], based on the conclusion of the present study, the overall effect of this surgical technique seems beneficial for patients in nationwide use. In assuring future proficiency and patient safety, systematic training of new surgeons carried out following international expert consensus is our best tool [25]. Continued national-level monitoring is needed as quality assurance. Another cause for the need of nationwide monitoring is the rapidly increasing use of robot-assisted MIO, with similarly beneficial results compared to OO in clinical trial settings as MIO in the TIME trial [11]. Reporting should be uniform within the ECCG framework, so that international comparisons are possible, facilitating the identification of points of improvement. As the implementation of MIO continues as the primary mode of resection for oesophageal cancer, future studies will show whether the complication profile of MIO further evolves over time.

In conclusion, the present study suggests significantly decreased postoperative complications in patients undergoing MIO in a population-based national cohort and provides reassurance that the nationwide implementation of MIO can be carried out safely.

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Ethics statement

The study has been approved by the ethical committee in Northern Ostrobothnia (EETMK 115/2016), and governmental agencies and hospital districts involved in the study. The requirement for individual consent was waived by the Finnish Institute for Health and Welfare.

Credit statement

Ville E.J. Sirviö: Conceptualization, Methodology, Writing – Original Draft, Visualization, Funding acquisition Jari V. Räsänen: Conceptualization, Methodology, Supervision Joonas H. Kauppila: Conceptualization, Methodology, Data curation, Formal analysis, Supervision, Project administration, Funding acquisition.

All authors: Validation, Investigation, Writing – Review and Editing.

Declaration of interest statement

Declaration of interest of the authors of "Surgical complications after minimally invasive oesophagectomy compared to open oesophagectomy for oesophageal cancer: A population-based, nationwide study in Finland": none.

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Appendix A. Supplementary data

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