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Long-term outcomes following minimally invasive and open esophagectomy in Finland: A population-based study

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ABSTRACT

Background: Studies of long-term survival after minimally invasive and open esophagectomy are needed. The aim of this study was to compare long-term outcomes following minimally invasive and open esophagectomy for esophageal cancer at the population level.

Methods: All patients undergoing minimally invasive (n = 159) or open transthoracic (n = 431) esophagectomy for esophageal cancer in Finland between 2004 and 2014 were identified from nationwide registries. Propensity score matching was used to create groups of 150 minimally invasive and open esophagectomies with balanced baseline characteristics (sex, age, comorbidity, center volume, year of surgery, histology, stage (local or locally advanced), and neoadjuvant therapy). The primary outcome was 1-year survival after surgery. Secondary outcomes were the 3-year, 5-year, and 90-day survival.

Results: The propensity matched 1-year survival rate was 85.3% after minimally invasive and 74.7% after open esophagectomy (adjusted HR 0.53, 95% CI 0.31–0.89; P = 0.0174). At 3 years, those were 68.7% and 55.6% (adjusted HR 0.62; 95% CI 0.43–0.91; P = 0.0144), respectively; at 5 years, survival rates were 61.8% and 51.9% (adjusted HR 0.68, 95% CI 0.47–0.97; P = 0.0347). The 30- and 90-day survival rates after minimally invasive and open surgery were 99.3% vs. 98.0% and 97.3% vs. 92.0%, respectively, without statistical significance.

Conclusions: In this population-based propensity matched study, minimally invasive esophagectomy was associated with improved long-term survival. Due to multiple confounding factors replication studies are needed.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related mortality [1], and surgery remains the primary treatment modality for early stage and locally advanced disease [2]. The use of neoadjuvant therapy has improved the long-term results in locally advanced disease [3]; yet, even after complete tumor resection, the 5-year survival has remained under 40% [4]. Esophagectomy is an extensive operation with high 90-day mortality around 7–9% [5,6], and one-year mortality around 30% at the population level affecting also the long-term results [7,8]. To reduce surgery-associated morbidity and mortality, minimally invasive esophagectomy (MIE) has been introduced [9]. Several single center series and one randomized study suggest that MIE reduces postoperative morbidity, shortens the hospital stay, and improves patient satisfaction [9–12]. These short-term advantages could suggest improved long-term survival. However, the 30-day mortality rates were similar in population-based studies from the United Kingdom, Japan, and the Netherlands comparing MIE and open esophagectomy (OE)

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[13–15]; while, a lower 90-day mortality was reported for MIE in a population-based study from Finland and Sweden [16].

Only a few reports have compared mid- or long-term results between the approaches. In a large cohort study from the United States, similar 3-year survival rates were reported after MIE and OE [17]. A single randomized controlled trial has been performed, reporting 3-year overall survival rates of 50.5% after MIE and 40.4% after OE [18], suggesting the oncologic outcome after MIE is at least comparable to OE. No population-based studies comparing long-term survival have been reported. The aim of this study was to report the long-term survival after MIE and transthoracic OE for esophageal cancer in an unselected nationwide population.

Methods

Study design

All patients who underwent MIE or transthoracic OE for cancer of the esophagus or gastroesophageal junction in Finland between January 1, 2004 and December 31, 2014 were eligible for this population-based, nationwide cohort study. The primary outcome of interest was the 1-year survival. Secondary outcomes were survival at 3 years, 5 years and 90 days after surgery.

Data collection

Residents in Finland have unique 11-digit registration numbers, allowing definite identification of patients from administrative databases and health data registries. All patients aged ≥18 years who underwent esophagectomy between January 1, 2004 and December 31, 2014 were retrospectively identified from the Care Register for Healthcare in Finland, which is an obligatory, nationwide registry including data on all hospital admissions that is run by The National Institute for Health and Welfare of Finland. Discharge diagnoses (International Classification of Diagnosis/ICD-10) and operational codes (Nordic Classification of Surgical Procedures) were obtained. Data on cancer histology (ICD03 classification), stage, and the use of neoadjuvant chemotherapy or chemoradiotherapy were obtained from the Finnish Cancer Registry. This obligatory and nationwide registry receives notifications of tumors independently from multiple sources at different phases of the disease resulting in more than 99% coverage [19]. Patients' mortality data were obtained from the nationwide and obligatory cause of death registry held by Statistics Finland. Follow-up ended five years after operation or on December 31, 2016 whichever came first. All surgery patients with primary malignant neoplasms of the esophagus or gastric cardia (ICD-10 codes C15 or C16.0) in the cancer registry were included in the study. The primary MIE approach in Finland was laparoscopy and thoracoscopy with intrathoracic anastomosis [20,21]. Cervical anastomosis was used only in highly selected cases. Of 565 identified open esophagectomies, 184 were transhiatal. Between open transhiatal and transthoracic esophagectomy, no statistically significant differences were detected in survival at 90 days (89.3% vs. 93.8%), or at 1 year (74.7% vs. 78.7%), 3 years (50.5% vs. 54.9%), or 5 years (40.9% vs. 46.4%), respectively. To avoid possible bias due to heterogeneity in operative techniques, transhiatal operations were excluded from the analyses.

The Charlson comorbidity index (CCI) was calculated from diagnoses in the registries according to a previously used algorithm [22], excluding esophageal and gastric cancers. Tumor stage was classified as local, locally advanced, or unknown, based on the classification recorded in the Finnish Cancer Registry. According to the AJCC 7th edition, locally advanced was defined as ≥ T3 and/or N1 disease. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016), Finnish Cancer Registry, and Statistics Finland (TK53-1410-15) approved the study.

Statistical analysis

Effect sizes in baseline characteristics between groups were evaluated by standardized difference scores [23]. Differences between groups were studied by Chi squared test, Mann-Whitney *U* test or T-test as appropriate. A cut-off points of ≥3 resections/year and study year ≥2009 based on CART (classification and regression tree) −analysis with one-year mortality and MIE usage as endpoints, respectively, were used to separate centers. Propensity score based on baseline characteristics (Table 1) was created with logistic regression. Score was used for appropriate local optimal 1:1 caliber matching with 0.20 caliper width of the logit of the standard deviation resulting to matched groups [24].

Survival was studied using the Kaplan-Maier method and Cox regression. Cox models evaluating the association of MIE with survival were adjusted for baseline characteristics: sex, age, CCI, center volume, year of surgery, histology, stage and use of neoadjuvant chemo or chemoradiotherapy. Effect modification between MIE usage and co-variables was studied using interaction term analysis. Follow-up was calculated for survivors.

Results are given as the mean, median, percentage, or hazard ratio (HR) with 95% CI or ±SD. A P value < 0.05 was considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) or SPSS 24.0 (CART-analysis).

Results

In the study period in Finland, the number of primary esophageal resection for cancer was 590. Of these, 159 were MIEs and 431 OEs. Seven hospitals performed only open surgery and six both OEs and MIEs. Of the 159 MIE patients, 96% (n = 153) had surgery in two hospitals, and 67% of the OE patients (n = 288) underwent surgery in three hospitals. The median number of esophagectomies due to esophageal cancer per center was 2.4 per year during the study period, when transhiatal procedures were excluded. Patients treated with MIE were more likely to have more comorbidities, adenocarcinoma and locally advanced disease treated with neoadjuvant chemotherapy (Table 1). Patients in the OE group were more often diagnosed with squamous cell carcinoma with no difference in the rate of preoperative chemoradiation between the two groups (Table 1). Propensity score matching resulted in groups of 150 MIEs and 150 transthoracic OEs with balanced baseline characteristics (Table 1).

The overall survival after esophageal resection for cancer was 80.0% at 1 year, 62.1% at 3 years, and 56.9% at 5 years in the matched cohort and 80.3%, 58.7%, and 50.7%, respectively, in the original cohort. The mean follow-up in propensity matched cohort was 1462 ± 387 days with no difference between MIE and OE groups (1469 ± 389 vs. 1454 ± 386 days, respectively, p = 0.803). In the original cohort, the mean follow-up in MIE and OE groups were 1454 ± 389 and 1565 ± 364 days (p = 0.016).

One-year survival

In the propensity matched cohort, the 1-year survival was 85.3% after MIE and 74.7% after OE (Fig. 1). The MIE was associated with improved survival with adjusted HR 0.53 (95% CI 0.31–0.89), Table 2. Association of MIE with lower mortality hazard was not modified by age (interaction p = 0.246), sex (p = 0.369), CCI-score (p = 0.244), stage (p = 0.817), morphology (p = 0.671), chemotherapy (p = 0.570), chemoradiotherapy (p = 0.981), year of surgery (p = 0.652), or center volume (p = 0.973).

Table 1
Features of the patients that underwent minimally invasive or open transthoracic esophagectomy for esophageal cancer in Finland in 2004–2014. Baseline characteristics are provided separately for the original cohort and propensity score matched cohort.

Variable	Original cohort			Matched cohort (caliper matching)		
	Minimally invasive n = 159	Open n = 431	Standardized difference[a]	Minimally invasive n = 150	Open n = 150	Standardized difference[a]
Age, years (SD)	64.2 (9.2)	63.3 (8.8)	0.09	63.9 (9.2)	64.3 (8.9)	0.03
Male sex	125 (78.6%)	329 (76.3%)	0.05	119 (79.3%)	119 (79.3%)	0.00
Charlson comorbidity score			0.19			0.08
0	116 (73.0%)	339 (78.7%)		111 (74.0%)	107 (71.3%)	
1	21 (13.2%)	58 (13.5%)		20 (13.3%)	24 (16.0%)	
≥2	22 (13.8%)	34 (7.9%)		19 (12.7%)	19 (12.7%)	
Tumor histology			0.36			0.12
Adenocarcinoma	122 (76.7%)	263 (61.0%)		113 (75.3%)	109 (72.7%)	
Squamous cell carcinoma	27 (17.0%)	138 (32.0%)		27 (18.0%)	26 (17.3%)	
Other[b]	10 (6.3%)	30 (7.0%)		10 (6.7%)	15 (10.0%)	
Stage			0.29			0.04
Local	19 (12.0%)	86 (20.0%)		19 (12.2%)	20 (13.3%)	
Locally advanced	108 (67.9%)	236 (54.8%)		99 (66.0%)	100 (66.7%)	
Unknown	32 (20.1%)	109 (25.3%)		32 (21.3%)	30 (20.0%)	
Neoadjuvant therapy						
Chemotherapy	82 (51.6%)	123 (28.5%)	0.48	73 (48.7%)	68 (45.3%)	0.07
Chemoradiotherapy	26 (16.4%)	89 (20.7%)	0.11	26 (17.3%)	31 (20.7%)	0.09
Year of surgery ≥2009[c]	152 (95.6%)	246 (57.1%)	1.02	143 (95.3%)	143 (95.3%)	0.00
Center volume ≥3 resections/year[d]	137 (86.2%)	330 (76.6%)	0.25	129 (86.0%)	125 (83.3%)	0.07

SD, standard deviation.
[a] Standardized difference = difference in means or proportions divided by standard error; imbalance defined as absolute value greater than 0.20.
[b] In a total of 40 cases no specific histology of the cancer was reported, or histology could not be determined (undefined carcinoma).
[c] Year of surgery was included in the analysis as continuous variable.
[d] Based on CART analysis.

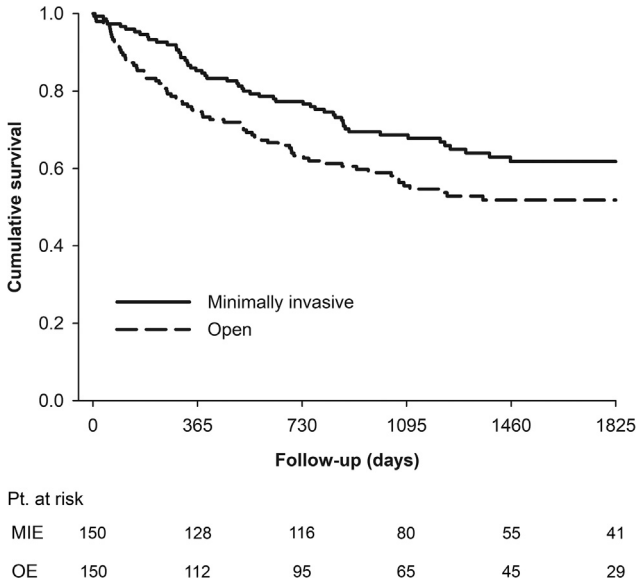

Fig. 1. Survival of patients treated with minimally invasive (solid line) or open (dashed line) esophagectomy for esophageal cancer in propensity score matched groups.

In the original cohort, survival rates were 84.9% and 78.7% (adjusted HR 0.56, 95% CI 0.34–0.91), Fig. 2, Table 2.

Three-year survival

In the propensity matched cohort, the 3-year survival was 68.7% after MIE and 55.6% after OE (Fig. 1). The MIE was associated with improved survival with adjusted HR 0.62 (95% CI 0.43–0.91), Table 2. Association was not modified by co-variables (Table 1; interaction p-values >0.244).

In the original cohort, survival rates were 69.2% and 54.9% (adjusted HR 0.59, 95% CI 0.42–0.83), Fig. 2, Table 2.

Five-year survival

In the propensity matched cohort, the 5-year survival was 61.8% after MIE and 51.9% after OE (Fig. 1). The MIE was associated with improved survival with adjusted HR 0.68 (95% CI 0.47–0.97), Table 2. Association was not modified by co-variables (Table 1; interaction p-values >0.185).

In the original cohort, survival rates were 62.6% and 46.6% (adjusted HR 0.62, 95% CI 0.45–0.86), Fig. 2, Table 2.

Short-term survival

For the propensity score matched cohort, survival at 30-days was 99.3% after MIE and 98.0% after OE, and at 90-days 97.3% and 92.0%, respectively, without statistical significance (Fig. 1, Table 2). In the original cohort, survival rates at 30-days were 98.7% and 98.1%, at 90-days, rates were 96.9% and 93.7% (Fig. 2, Table 2).

Discussion

In this national population-based cohort study assessing survival after MIE and OE for esophageal cancer, MIE was associated with an improved 1-year survival. In secondary analysis, the survival advantage remained significant at the 3- and 5-year follow-up.

This study is, to our knowledge, the first to compare the long-term survival of MIE and OE for esophageal cancer in a population-based setting. Previously, several randomized trials compared minimally invasive and traditional techniques in other gastrointestinal cancers, such as colon cancer, with no short- or long-term survival differences [25]. The 30-day and 3-year mortality rates of 1–2% and 15–20% after colon cancer surgery [25] are more than doubled following esophageal resection [13,18]; therefore, the results of colon surgery are hardly applicable to esophageal cancer surgery. Only one randomized controlled study has been published comparing MIE and OE [12,18]. This TIME-trial

Table 2
Hazard ratios (HR) with 95% confidence intervals (CI) of all-cause mortality comparing minimally invasive and open transthoracic esophagectomy for esophageal cancer at 90-days, 1-year, 3-year and 5-years after surgery. Results of propensity score matched cohort (n = 300) and original cohort (n = 590) are presented separately.

	Open esophagectomy	Minimally invasive esophagectomy			
		Matched Cohort		Original Cohort	
	HR (95% CI)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
90-day mortality					
Crude	1 (reference)	0.33 (0.11–1.02)	0.0535	0.50 (0.19–1.29)	0.1525
Adjusted[a]	1 (reference)	0.37 (0.11–1.05)	0.0613	0.40 (0.15–1.09)	0.0717
1-year mortality					
Crude	1 (reference)	0.53 (0.31–0.89)	0.0172	0.67 (0.43–1.05)	0.0819
Adjusted[a]	1 (reference)	0.53 (0.31–0.89)	0.0174	0.56 (0.34–0.91)	0.0192
3-year mortality					
Crude	1 (reference)	0.62 (0.43–0.91)	0.0145	0.62 (0.45–0.85)	0.0033
Adjusted[a]	1 (reference)	0.62 (0.43–0.91)	0.0144	0.59 (0.42–0.83)	0.0028
5-year mortality					
Crude	1 (reference)	0.67 (0.47–0.96)	0.0305	0.63 (0.47–0.84)	0.0021
Adjusted[a]	1 (reference)	0.68 (0.47–0.97)	0.0347	0.62 (0.45–0.86)	0.0041

[a] Adjustment for age, sex, Charlson comorbidity index, center volume, year of surgery, histological type, stage, and neoadjuvant therapy (Table 1).

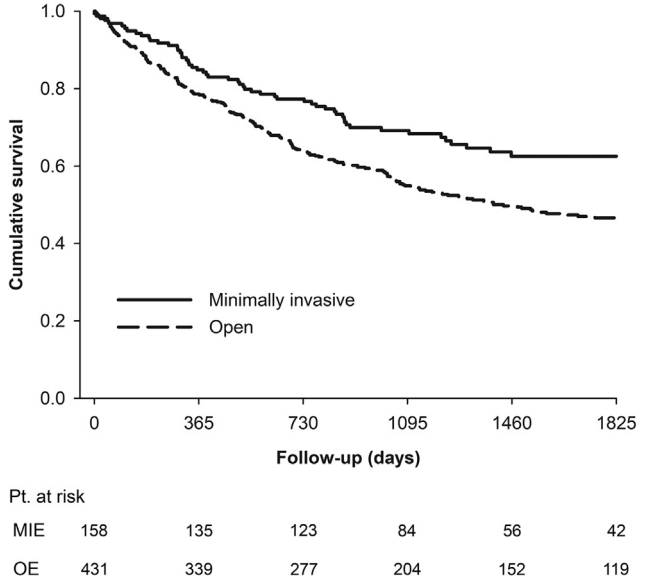

Fig. 2. Survival of patients treated with minimally invasive (solid line) or open (dashed line) esophagectomy for esophageal cancer in the original cohort.

mainly aimed to assess short-term morbidity, and randomized only 59 patients to the MIE group and 56 to the OE group. Study showed a lower rate of postoperative pulmonary complications and a non-significant survival benefit at 3-years after MIE (50.5% vs. 40.4%) among patients treated with neoadjuvant therapy and surgery. In our study, including patients in all stages, the 3-year survival was 69.2% after MIE and 54.9% after OE, a difference similar to that reported in the TIME-trial.

The population-based design, including complete follow-up of all patients, is the main strength of our study. Nationwide analysis with inclusion of all esophagectomies for cancer provides an opportunity to assess the differences between MIE and OE in general surgical practice, which might not be the case in reports from high-volume centers or in randomized clinical trials with strict inclusion criteria. The retrospective observational study design can, however, cause confounding. To reduce this, we took into account various known confounding variables, such as sex, age, comorbidity, center volume, year of surgery, histology, tumor stage, and received neoadjuvant therapy. Detailed information on the stage was missing from 23.9% of patients and this can affect the results. Furthermore, tumor size could not be adjusted for. Due to shortcomings in the TNM data collection, we could separate only local and locally advanced disease. Locally advanced disease included, however, only resectable tumors $\geq$ T3 and/or N $\geq$ 1, as in the European Society for Medical Oncology (ESMO) guidelines [2]. According to current ESMO guidelines, neoadjuvant chemoradiotherapy (squamous cell and adenocarcinoma) or neoadjuvant/perioperative chemotherapy (adenocarcinoma only) is recommended for locally advanced disease [2]. Due to lack of data, we were not able to adjust for adjuvant or palliative chemo/chemoradiotherapy [26]. Since our study material started in 2004, there have been some variations in treatment protocols between centers. Nearly all MIEs were performed in two high-volume hospitals by high-volume surgeons; whereas, OE cases were divided more evenly around the country, which could cause confounding [27,28]. Patients treated with MIE more often received neoadjuvant therapy, which can be due to more updated treatment protocols, better preoperative staging (for example standard use of positron emission tomography), and therefore, better patient selection. It is possible that experience affects survival rather than technique itself. To minimize the effect of these confounding factors, neoadjuvant therapy was included in the adjusted model, and CART-analysis was performed to include differences in center volumes. Due to the lack of separate coding, we could not differentiate totally minimally invasive surgery from a hybrid procedure. The standard in the two high-volume centers for MIE is a combined thoracoscopic and laparoscopic approach with around 10% being hybrid approaches [20]. The exact number of missing hybrid procedures, and also the inclusion of the learning curve phase of MIE in Finland should lessen, rather than exaggerate the beneficial effects of MIE. However, it is noteworthy that confounding factors are complex and adjustments provide only the best available model to compare the two surgical treatments.

We present results showing a significant survival advantage after MIE, compared with OE, even after adjusting for confounding variables and propensity score matching. Regardless of adjusting, MIE is likely to be associated with better staging and patient selection, multimodality therapy and technical expertise which might explain the survival advantage instead of the technique itself. There are, however, several potential explanations for the possibility of technique-related benefit. First, lower morbidity and improved short-term survival after MIE has an effect on long-term survival [12]. In population-based studies, no difference has been observed in the 30-day mortality between MIE and OE [13–15]. However, after esophageal surgery, 90-day mortality is a more representative short-term outcome measure [29]. In our study, 90-day survival

was non-statistically improved after MIE with the absolute difference being 5.3% in matched cohort. Improved 90-day survival was previously reported in a population-based study from Finland and Sweden, which also included patients from the current study [16]. The survival difference seems to increase during the first postoperative year, possibly due to increased morbidity and worse quality of life after OE. In the only randomized study, the 1-year mortality difference between the modalities was 8%, which was not statistically significant [18]. Overall, the 1-year mortality at the population level or even in high-volume centers has been 25–30% [7,8,30] comparable to 21.3% after OE in this study. The previously reported mortality in locally advanced disease treated with neoadjuvant therapy and MIE in Finland was around 15% at 1 year [20]. The absolute survival difference in locally advanced disease between approaches at 5 years in that relatively small single center study was 15% (56% after MIE and 41% after OE; P = 0.321) [20]. The overall results in Finland reported in the current population-based study with a 10.6% absolute mortality difference at 1 year and 13.1% difference at 5 years between MIE and OE in matched cohort, are very similar to those previously reported in locally advanced disease [18,20]. Therefore, it seems that MIE significantly reduces the long-term mortality rates. Reasons for survival difference between MIE and OE beyond 1-year mark remain speculative. There is, however, evidence of association with perioperative systemic inflammation, higher recurrence rates and decreased survival, even after exclusion of infectious complications [31,32]. More importantly, postoperative complications after open esophagectomy are related to timing of death due to recurrence [33,34]. Surgical trauma and higher morbidity after OE could therefore explain the long-term survival difference between the treatment modalities.

Conclusions

The results from this population-based study from Finland indicated improved long-term survival after MIE. These findings support the use of a minimally invasive approach as the primary surgical method for esophageal cancer. Due to the complexity of confounding factors in this study, one should interpret the results critically and additional studies are needed.

Declarations of interest

None.

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