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Open versus minimally invasive esophagectomy: clinical outcomes for locally advanced esophageal adenocarcinoma

Juha Kauppi · Jari Räsänen · Eero Sihvo · Riikka Huuhtanen · Kaisa Nelskylä · Jarmo Salo

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Abstract
Background We compared oncologic and surgical outcome between minimally invasive esophagectomy (MIE) and the Ivor Lewis-type open approach (OE) in the treatment of locally advanced esophageal adenocarcinoma (EAC).
Materials and methods Of 284 patients undergoing surgery for EAC between 2003 and 2013, the 153 selected with locally advanced EAC were 74 MIEs and 79 OEs [median age, 66 for MIE, 63 for OE ($p = 0.009$)]. Neoadjuvant therapy was given to 82 % of MIEs and 78 % of OEs. In the OE group, 86 % was male, and in the MIE group, 78 %. Data assessed were oncologic, intraoperative, and postoperative.
Results Mortality at 30 days was 3 % for MIE and 1 % for OE; and 90-day mortality was 4 % for MIE and 5 % for OE. The complication rate for MIE was 50 %, and 60 % for OE ($p = 0.181$). The pneumonia rate was 18 % for MIE and 19 % for OE; leak rate was 7 % for MIE and 6 % for OE; conduit necrosis was 0 for MIE and 3 % for OE; and rate of airway-conduit fistula was 3 % for MIE and 1 % for OE. Median blood loss (MIE 300 vs. OE 800, $p < 0.0001$), overall stay (MIE 13 vs. OE 14, $p = 0.040$), and harvested lymph nodes (MIE 20 vs. OE 22, $p = 0.021$) all were in favor of MIE. Median ICU stay and operative time did not differ. Neither did overall (OS) nor recurrence-free (RFS) 3-year survival differs significantly (MIE 64 % vs. OS OE 49 %, MIE 57 % vs. RFS OE 53 %).
Conclusions In our institution, MIE appears to produce oncologic and survival results similar to those of OE. Shorter length of stay and less operative blood loss may reduce costs for MIE.

Keywords Esophageal adenocarcinoma · Surgery · Minimally invasive esophagectomy · Open esophagectomy

In locally advanced esophageal adenocarcinoma (EAC), meaning muscularis propria invasion or lymph-node involvement, 5-year survival remains between 15 and 35 % [1]. Neoadjuvant chemo- or chemoradiotherapy has improved results [2, 3]. Radical esophagectomy has a low mortality rate in high-volume centers, but morbidity rates are substantial [4]. Minimally invasive esophagectomy (MIE) aims to reduce morbidity by avoiding large incisions and achieving the same surgical radicality as transthoracic en bloc esophagectomy (OE). Luketich et al. [5], in a benchmark series with 1,000 consecutive MIEs, reported a 1-month operative mortality of 1.7 % and a leak rate of 5 %. Their median number of dissected lymph nodes was 21. Meta-analyses of retrospective series of MIE suggest a surgical outcome equivalent to that of open surgery [6–8], with fewer pulmonary complications and a shorter hospital stay. A recent randomized trial by Biere et al. [9], with a short follow-up, shows reduced risk for postoperative pulmonary infection in MIE, along with better short-term quality of life. Nafteux et al. [10], in treatment of early

J. Kauppi · J. Räsänen · E. Sihvo · J. Salo (✉)
Department of General Thoracic and Esophageal Surgery, Heart and Lung Center, Helsinki University Central Hospital, HUS, Haartmaninkatu 4, P. O. Box 340, Helsinki 00029, Finland
e-mail: jarmo.salo@hus.fi

R. Huuhtanen
Cancer Center, Helsinki University Central Hospital, Helsinki, Finland

K. Nelskylä
Department of Anesthesiology and Intensive Care, Helsinki University Central Hospital, Helsinki, Finland

EAC, have demonstrated in MIE lower morbidity than for OE and comparable long-term follow-up. Our study aims to test the safety and oncologic results of the MIE technique compared to the traditional OE approach, in treatment of locally advanced EAC.

Patients and methods

This retrospective study comprised patients consecutively undergoing surgery in 2003–2013 for adenocarcinoma of the esophagus or gastroesophageal junction at the Clinic of General Thoracic and Esophageal Surgery, Heart and Lung Center of Helsinki University Central Hospital in Finland. Of the 284 patients having undergone surgery with curative intent, all had locally advanced (stage > 2b) [11] EAC, and their surgery was completed with the MIE ($n = 74$) or OE ($n = 79$) technique (Table 1). Excluded were patients with transhiatal resection or stage-IV disease. Patients with conversion to thoracotomy or laparotomy and patients with a planned hybrid operation were classified as MIE, on an intention-to-treat basis. All preoperative, operative, and postoperative follow-up and survival data served for our analysis. The institutional review board at Helsinki University Central Hospital approved the review of this patient data.

Table 1 Characteristics of patients undergoing minimally invasive esophagectomy (MIE) and open esophagectomy (OE)

	OE ($n = 79$)	MIE ($n = 74$)	*p*
Age (range)	63 (39–82)	66 (51–85)	0.009
BMI	25.4 (17.4–43.4)	25.6 (17.1–37.6)	0.419
FEV1%	87.5 (58–133)	92 (57–127)	0.673
Male (%)	68 (86)	59 (78)	0.279
Comorbidites (%)			
Liver	0	4 (5)	0.036
Pulmonary	14 (24)	12 (16)	0.804
Neurologic	5 (6)	6 (8)	0.670
Crea > 150	3 (4)	4 (5)	0.634
Diabetic	13 (16)	17 (23)	0.310
Cardiac	17 (22)	14 (19)	0.689
ASO	7 (9)	5 (7)	0.629
APM	8 (10)	8 (10)	0.818
cTNM (%)			
IIB	25 (32)	28 (38)	0.421
IIIA	49 (62)	42 (57)	0.507
IIIB	0	0	
IIIC	5 (6)	2 (3)	0.283
IV	0	0	
Neoadjuvant (%)	62 (78)	61 (82)	0.538
Chemo	49 (62)	55 (74)	0.103
Radiation	0	1 (1)	0.300
Radiochemo	12 (15)	3 (4)	0.048

APM another primary malignancy, *ASO* atherosclerotic vasculopathy, *BMI* body mass index, *cTNM* clinical Ajcc 2007 classification, *Crea* serum creatinine, *FEV1%* forced expiratory volume percentage

Preoperative staging was as described in our earlier publication [12]. Detailed evaluation of pulmonary, cardiac, renal, and liver function allowed assessment of the patients' ability to tolerate radical esophagectomy and neoadjuvant treatment. Patients also visited a nutritional therapist during neoadjuvant therapy. Those with clinical stage 2B or higher [11] were offered neoadjuvant therapy lasting 4–8 weeks, followed by radical esophagectomy. Surgery alone was offered in cases showing risk for a multimodality approach (frailty, renal insufficiency). Approach of operation (OE/MIE) was surgeon dependent. Two of the authors (JR and ES) with minimally invasive surgery experience performed MIE and the others OE. Before MIE program, all surgeons performed OE.

Since 2007, eligible patients were treated with epirubicin–oxaliplatin–capecitabine (EOX) neoadjuvant chemotherapy [13]. Prior to then, selected patients received various types of chemo- and radiotherapy. 3-week EOX cycles included an intravenous (iv) bolus of epirubicin (50 mg/m^2 of body surface area) plus an iv infusion of oxaliplatin (130 mg/m^2), both on day 1. Oral capecitabine (1,000–1,250 mg/m^2/day) was given on days 1–21. Chemoradiotherapy consisted of 2 cycles of platin- and 5-fluorouracil-based therapy over 5–6 weeks. Chemosensitization was followed by a 45-gy total dose of radiation to the tumor and regional nodes, in 1.8-gy daily portion.

Preoperative measures were the same in both patient groups, and both techniques included proximal gastrectomy and distal esophagectomy with two-field lymphadenectomy and creation of a 5- to 6-cm-wide gastric tube. Esophagogastric anastomosis was done mainly intrathoracally in both groups, stapled anastomosis with a DST™ EEA™ circular 25-mm stapler (Covidien, Mansfield, MA), and hand-sewn anastomosis in two layers with absorbable 4-0 sutures (PDS). MIE and OE are described elsewhere [14, 15].

Follow-up consisted of upper endoscopy and computed tomography scanning of the thorax, abdomen, and pelvis every 6 months after surgery for 2 years, and annually for up to 5 years at an outpatient clinic.

Statistical analysis

All analyses were performed with PASW statistics 18.0 for MAC (SPSS Inc. Chicago, IL). All quantitative data were expressed as median with range. Comparisons of categorical variables were made using Chi-square test and continuous variables using the Mann–Whitney *U* test. Survival rates were estimated according to the Kaplan–Meier and Cox proportional hazards model. Statistical comparisons of survival between groups of patients were performed with a log-rank test. Overall and recurrence-free survival rates were calculated from date of operation. The endpoint was defined as death from any cause or first recurrence of EAC. Significance level was $p < 0.05$.

Results

Overall mortality within 90 days was seven patients (5 %), and 1-month mortality was three (2 %). 1-month mortality resulted from airway-conduit fistula in the OE group and in the MIE group by pulmonary embolism and anastomotic leakage with mediastinitis. Ninety-day mortality resulted from two recurrent cancers and one pneumonia in the OE group and an airway-conduit fistula in the MIE group. Overall rate of complications was 60 % for OE and 50 % for MIE ($p = 0.181$). For details, see Table 2.

Table 2 Complications

	OE $n = 79$ (%)	MIE $n = 74$ (%)	p
Postoperative <30 day			
Overall	48 (60)	37 (50)	0.181
Resp. insuff.	15 (19)	11 (15)	0.521
Pneumonia	15 (19)	13 (18)	0.851
Empyema	7 (9)	3 (4)	0.238
Pulm. emb.	5 (6)	5 (7)	0.915
Cardiac	20 (25)	14 (19)	0.341
Abdominal	4 (5)	4 (5)	0.909
Neurologic	10 (13)	1 (1)	0.007
Chylous leak	8 (10)	3 (4)	0.219
Minor leak	5 (6)	5 (7)	0.474
Airway-conduit fistula	1 (1)	2 (3)	0.514
Conduit necrosis	2 (3)	0	0.171
Vocal cord palsy	3 (4)	0	0.093
Renal insuff. (cr > 120)	1 (1)	2 (3)	0.514
Intraoperative			
Major bleed	0	3 (4)	0.071
Airway injury	0	2 (3)	0.171
Conduit injury	1 (1)	4 (5)	0.150
Early (30-day) re-operations	9 (11)	8 (11)	0.581
Late complications (>30 day)			
Stricture	8 (10)	3 (4)	0.053
Hiatal herniation	2 (3)	2 (3)	0.946
Ventral herniation	3 (4)	0	0.081
Vocal cord palsy	1 (1)	0	0.332
Intestinal fistula	1 (1)	0	0.332

Postoperative pneumonia was defined as typical findings in chest X-ray or in chest computed tomography and rise in markers of infection (fever, c-reactive protein, white blood cell count), anastomotic leak as an anastomotic defect with preserved conduit vitality in upper GI endoscopy. One patient in the MIE group died of leakage and mediastinitis, but all others were stented with success or treated conservatively. Conduit necrosis was defined as loss of vitality of an anastomotic area causing leakage and sepsis. Two patients in the OE group had their conduits resected and repaired with a colon substitute at a later stage successfully. Airway-conduit fistula was defined as an anastomotic leakage with fistulization to either bronchi or trachea. One patient in the OE group died of airway fistula and ARDS within 1 month and one other in the MIE group within 3 months after surgery. The other patient with fistula to the airways in the MIE group was successfully repaired with a latissimus dorsi flap.

Details of these operations are given in Table 3. Blood loss during OE surgery was 800 (110–4,000) ml and for MIE 300 (50–3,000) ml ($p < 0.0001$). ICU stay was 2 (1–63) days for MIE, and 3 (1–35) days for OE ($p = 0.255$). Overall length of stay was 14 (9–63) days with OE and 13 (6–87) days with MIE ($p = 0.040$).

For details of postoperative pathologic data, see Table 4. Median follow-up was 28 (0–116) months. There was no significant difference in 3- (OE 49 % vs. MIE 64 %) or 5-year (OE 41 % vs. MIE 56 %) survival ($p = 0.321$) (Fig. 1). Recurrence-free survival for 3 years was 53 % for OE and 57 % for MIE ($p = 0.911$) (Fig. 2). Time to first

Table 3 Characteristics of OE + MIE operations

	OE $n = 79$ (%)	MIE $n = 74$ (%)
Primary anastomosis		
Intrathoracal	70 (89)	72 (99)
Not done	0	1 (1)
Hand-sewn	76 (96)	3 (4)
Stapled	3 (4)	70 (96)
Primary conduit		
Stomach	72 (91)	72 (99)
Colon (IP)	2 (3)	1 (1)
Roux	5 (6)	0
Time of operation (MIN)	367 (230–679)	359 (216–684)
Conversion to open	NA	12/74 (16)
Hybrid operations		
Laparoscopy/TT	NA	3 (4)
VATS/LT		6 (8)

LT laparotomy, *MIE* minimally invasive esophagectomy, *MIN* minute, *ML* milliliter, *NA* not applicable, *OE* open esophagectomy, *IP* interposition, *TT* thoracotomy, *VATS* video-assisted thoracoscopic surgery

Table 4 Postoperative pathologic data

	OE $n = 79$ (%)	MIE $n = 74$ (%)
pTNM		
0	8 (10)	9 (12)
IA	7 (9)	9 (12)
IB	12 (15)	6 (8)
IIA	4 (5)	0
IIB	15 (19)	21 (29)
IIIA	11 (14)	11 (15)
IIIB	8 (10)	7 (10)
IIIC	11 (14)	8 (11)
IV	2 (3)	0
Complete response	8 (10)	9 (12)
Adjuvant therapy	28 (35)	28 (38)
EOX	18 (23)	24 (33)
Other chemo	5 (6)	1 (1)
Radiotherapy	1 (1)	0
Chemoradiotherapy	4 (5)	3 (4)
Recurrence rate	35 (44)	25 (34)
Local	5 (6)	1 (1)
Local & distal	5 (6)	4 (5)
Distal	25 (32)	20 (27)

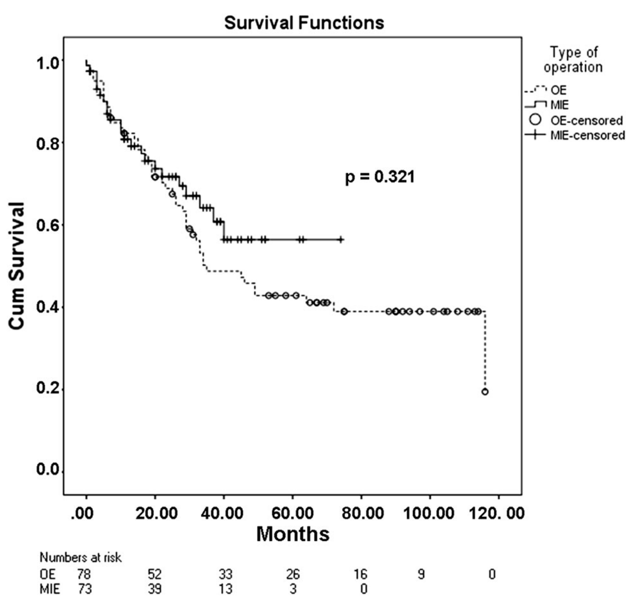

Fig. 1 Overall survival (months) after surgery for locally advanced esophageal adenocarcinoma by either open (OE) or minimally invasive (MIE) esophagectomy. Kaplan–Meier, Log-rank

detected recurrence was 11 (2–29) months in the OE group and 9.5 (1–37) months in the MIE group ($p = 0.525$) (Fig. 3). Rate of R1 resection in the OE group was 2 versus 1 % in MIE ($p = 0.522$). Rate of harvested nodes was less

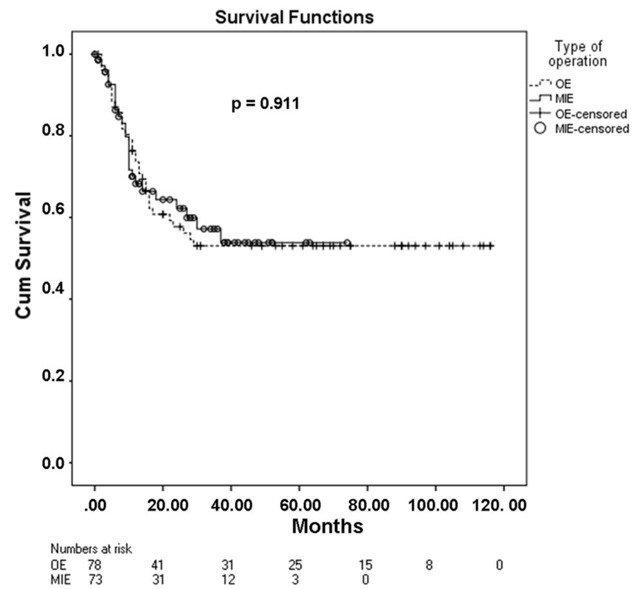

Fig. 2 Recurrence-free survival (months) after surgery for locally advanced esophageal adenocarcinoma by either open (OE) or minimally invasive (MIE) esophagectomy. Kaplan–Meier, Log-rank

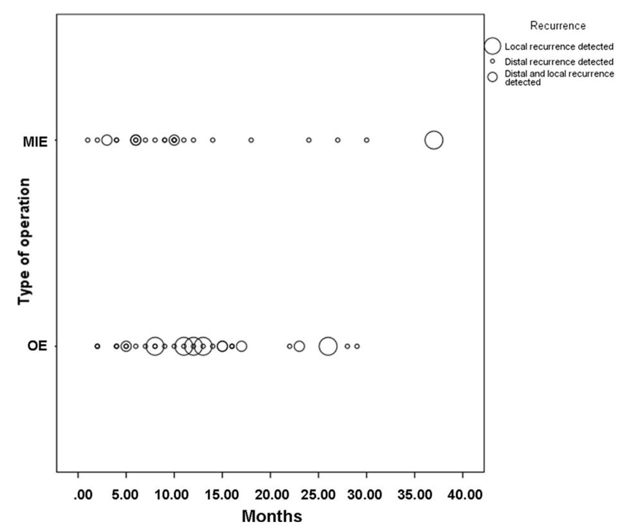

Fig. 3 Timing of first recurrence after surgery for locally advanced esophageal adenocarcinoma by either open (OE) or minimally invasive (MIE) esophagectomy

in the MIE, 20 (4–49) than in the OE, 22 (8–58), ($p = 0.021$). Overall, male gender and pathological stage over 2B remained significant and therefore independent predictors (Table 5).

Discussion

Here, we analyzed data gathered after a 10-year transition period from traditional open surgery to a minimally

Table 5 Multivariate analysis of factors affecting overall survival with Cox proportional hazards model

	Exp(B)	95 % CI	p
Operation type	0.859	0.505–1.460	0.574
Age	0.976	0.947–1.005	0.106
Neoadjuvant	0.980	0.531–1.808	0.984
Gender	0.546	0.301–0.988	0.046
Any complication	0.484	0.285–0.821	0.007
pTNM 2b	0.372	0.222–0.622	<0.0001

pTNM pathological AJCC 2007 classification

invasive technique in EAC. We began MIE surgery in 2007 gradually, with hybrid approaches, and in 2009 introduced totally mini-invasive operations with intrathoracic anastomosis.

Our most important finding is that in treatment of locally advanced EAC, the MIE technique appears equal to the traditional open technique in terms of cancer clearance and survival. MIE seems to offer the benefits of a shorter hospital stay and less surgical blood loss. Complication rates were similar. Despite this being our early series including our learning curve, we were able to achieve equal short-term results in treatment of adenocarcinoma of the esophagus and the GE junction.

Overall- and recurrence-free survival between the OE and MIE groups at 3 and 5 years did not differ significantly. After adjustment for age, sex, complications, and pathological stage in a Cox model, type of operation was non-significant. Patients having the open approach undergo obviously longer follow-up, and their long-term survival is therefore not yet comparable. A meta-analysis by Dantoc et al. [7] shows no significant difference regarding 1-, 3-, and 5-year overall survival between OE and MIE, results in line with ours. Thomson et al. [16] reviewed 221 adenocarcinoma patients' cases undergoing either the transthoracic (TTE) or thoracoscopic-assisted technique (TAE). They reported a 5-year distal recurrence rate of 43 % and a local recurrence rate of 4 % for TAE, and a 55 % distal and a 5 % local recurrence rate for TTE. These results are close to our 35 % distal and 1 % local recurrence rate for MIE, and 45 and 5 % rate for OE patients. Recurrence-free survival in Thomson's study [16] was 39 % at 5 years for TAE and 28 % for TTE, less than ours for both groups. The fact, that our patients underwent neoadjuvant therapy (OE 78 % and MIE 82 %), may explain these differences. Time to any first recurrence in their study was 12 (1–131) months, similar to our 11 months for OE and 9.5 months for MIE.

Outcome regarding lymph-node yield was slightly better in OE than in MIE. A meta-analysis by Dantoc et al. [7] reported the number of lymph nodes to be median (range) MIE, 16 (5.7–33.9), and OE, 10 (3.0–32.8), with a significant difference favoring MIE ($p = 0.04$). Other meta-analyses, however, [6, 17] showed no difference in number of dissected lymph nodes. Our number of dissected nodes falls well within the range in these studies. We prepared no nodes for the pathologist, so number of nodes examined may be biased.

No difference appeared in OR time or in ICU time; blood loss was significantly less and overall stay shorter for MIE as others also find [6, 18].

The total rate of complications has been reported as less for MIE, but the rate of serious complications is reported as similar for both operations [19, 20]. MIE patients were older and had had more liver disease than did patients in the OE group, which in part explains this small difference.

Rate of pulmonary complications, in MIE patients in most reports, is significantly lower [6, 19]. Our rate of pneumonia or respiratory insufficiency in both groups was similar. Verhage et al. [18] reviewed 10 case–control studies and reported a 15.1 % pneumonia rate for MIE and 22.9 % for OE. Few studies report on pneumonia as a specific complication, and their definitions of pulmonary complication are inconsistent. Our patient groups showed no difference in preoperative pulmonary function, in history of pulmonary disease, or in use of epidural analgesia, but MIE patients were older than patients with OE. Furthermore, comparing our results to those of other series remains difficult: criteria for respiratory complications may vary, and some studies report only major complications.

Our leakage rates (6 % OE vs. 7 % MIE) were similar, as in meta-analyses [6, 19] and in a recent randomized trial [9]. Delirium prolonging their ICU stay was significantly more frequent for OE patients (10 vs. 1, $p = 0.04$), probably explainable by greater stress from the more invasive approach. In a meta-analysis by Nagpal et al. [6], rates of vocal cord palsy between OE- and MIE patients did not significantly differ, in line with our findings.

Risk for early (<30 days) re-intervention was the same in both groups, 13 % for OE and 12 % for MIE ($p = 0.823$), not differing from the 2 to 20 % rate reported in a meta-analysis by Hanna et al. [8]. Late intervention was more frequent in the OE group, though not significantly. Anastomotic strictures were more frequently dilatated with hand-sutured anastomosis in patients in the OE group. Surgeons using cervical anastomosis meet a higher incidence of stricture in the MIE than in the OE category [21, 22]. On the other hand, one comparison of intrathoracic anastomoses between those hand-sutured and stapled found fewer strictures and postoperative dysphagia in the stapled group [23], in line with our results.

Obvious limitations of this study are its retrospective nature and our shorter follow-up of the MIE group. Overall, in terms of cancer recurrence, overall survival, and in intraoperative and postoperative outcome, results of MIE and OE are comparable. In this study, MIE offered benefits by its shorter overall stay, which could translate to less cost. Blood loss was also clearly less, which is in cancer surgery of benefit [24]. We conclude that MIE is a feasible technique in locally advanced disease and after neoadjuvant chemotherapy.

Disclosures Drs. Kauppi, Räsänen, Sihvo, Huuhtanen, Nelskylä, and Salo have no conflicts of interest or financial ties to disclose.

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