

Minimally Invasive Esophagectomy Provides Equivalent Oncologic Outcomes to Open Esophagectomy for Locally Advanced (Stage II or III) Esophageal Carcinoma

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Background: Minimally invasive esophagectomy (MIE) has been performed at specialized centers for 15 years, but few studies have looked at outcomes in patients with locally advanced cancers, and few studies have provided long-term survival comparison with Ivor Lewis esophagectomy (ILE) to determine oncologic benefit or equivalence of MIE.

Hypothesis: Minimally invasive esophagectomy for locally advanced esophageal carcinoma has similar oncologic outcomes to traditional open ILE with less associated short-term morbidity and mortality.

Design: Retrospective comparison of patients with stage II or III esophageal carcinoma undergoing 3-field MIE compared with open ILE.

Setting: University medical center.

Patients: From 1995 to 2009, 64 patients who underwent MIE (33 patients) or ILE (31 patients) with clinical stage II or III esophageal cancer were compared.

Main Outcome Measures: Primary end points included operative performance, morbidity, mortality, hospital stay, and survival.

Results: No differences were noted between the groups in demographics, neoadjuvant therapy use ($P=.22$), resection completeness (R0:R1) ($P=.57$), length of stay ($P=.59$), intensive care unit stay ($P=.36$), anastomotic leak ($P=1.0$), pulmonary morbidity ($P=.26$), and mortality ($P=1.0$). Median follow-up was 19 months for MIE and 17 months for ILE. Survival at 2 years was 55% for MIE (18 of 33 patients) and 32% for ILE (10 of 31 patients) while disease-free survival was 55% for MIE (18) and 26% for ILE (8).

Conclusions: Our survival analysis shows divergent curves that favor MIE but have not yet reached statistical significance. The oncologic outcomes of MIE are comparable to that of ILE 2 years after resection.

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ESTIMATES FROM THE NATIONAL Cancer Institute indicate that esophageal cancer contributes to 14 000 deaths annually.¹ Surgical resection of the esophagus remains the primary treatment for this disease. Since its first description by Ivor Lewis,² the combined thoracic and abdominal approach to esophageal resection has become a widely accepted approach for locally advanced esophageal carcinoma. Variations of this technique include en bloc esophagectomy and “radical” trans-thoracic esophagectomy. In randomized trials and large case series, mortality and morbidity of Ivor Lewis esophagectomy (ILE) is high.^{3,4} Over time, the mortality rate has decreased, but the morbidity rates remain high.

Minimally invasive esophagectomy (MIE) was introduced in the early 1990s with the hope of lessening the morbidity of esophagectomy without compromising the oncologic results of the open ILE. Although the number of single institution re-

ports on MIE have been increasing, there remain few reports comparing ILE and MIE. We have previously looked at the differences in perioperative outcomes of patients undergoing 3-field MIE as compared with open ILE.⁵ In this study, our objective was to determine whether MIE was an equivalent oncologic operation to ILE and whether intermediate survival was equivalent to that of ILE. This objective was examined by performing a retrospective cohort study comparing the survival and perioperative outcomes of MIE and ILE at a large university medical center.

METHODS

PATIENTS

Thirty-three patients underwent 3-field MIE for clinical stage II and III esophageal carcinoma at Oregon Health & Science University, Portland, from September 1, 2005, to March 31, 2009. These patients were compared with 31 historical control patients who had similar clinically staged esophageal carcinoma and who un-

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Table 1. Univariate Analysis of MIE and ILE for Locally Advanced Esophageal Cancer

Parameter	No. (%)		P Value
	MIE Group (n=33)	ILE Group (n=31)	
Age, mean (SD), y	63.8 (8.6)	62.3 (10.2)	.53
Sex (M/F)	31:2	25:6	.14
Body mass index, ^a median (IQR)	25.6 (23-28)	26.2 (24-34)	.59
ASA classification			
1	0	1 (3)	.70
2	7 (21)	8 (26)	
3	25 (76)	20 (65)	
4	1 (3)	2 (6)	
Clinical stage			
IIA	13 (39)	13 (42)	.52
IIB	2 (6)	3 (10)	
III	18 (55)	15 (48)	
Pathologic stage			
CPR	11 (33)	6 (19)	.16
I	2 (6)	0	
IIA	9 (27)	7 (23)	
IIB	4 (12)	2 (6)	
III	7 (21)	12 (39)	
IVA/IVB	0	4 (13)	
Total lymph nodes, median (IQR)	14 (6-16)	8 (3-14)	.01
Positive lymph nodes, median (IQR)	0 (0-1)	0 (0-3)	.05

Abbreviations: ASA, American Society of Anesthesiologists; CPR, complete pathologic response; ILE, Ivor Lewis esophagectomy; IQR, interquartile range; MIE, minimally invasive esophagectomy.

^aCalculated as weight in kilograms divided by height in meters squared.

derwent ILE between February 1, 1996, and July 31, 2007. A prospective database approved by our institutional review board was used to store and extract patient data. Patient and operative variables that were compared and previously reported included age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), American Society of Anesthesiologists classification (ASA),⁶ clinical stage, pathology, operative time, blood loss, intraoperative intravenous fluid requirement, length of hospital stay, and perioperative morbidity and mortality.⁵ End points that were compared in this study included completeness of resection, lymph node harvest, disease-free survival, and overall survival.

PREOPERATIVE EVALUATION AND PATIENT PREPARATION

Clinical staging was performed on all patients before surgery and included upper endoscopy, endoscopic ultrasonography, and radiolabeled fluorodeoxyglucose F18 positron emission tomography-computed tomography (PET-CT) of the chest, abdomen, and pelvis. The objective of our study was to compare outcomes of 3-field MIE with ILE for locally advanced esophageal cancer. Thus, patients with premalignant, local (stage I), and distant (stage IV) malignant disease were excluded from the study. Early-stage disease was treated with endoscopic resection or laparoscopic transhiatal esophagectomy; stage IV disease was treated with definitive chemoradiotherapy. Those with clinical stage II or III esophageal carcinoma were offered neoadjuvant chemoradiotherapy with definitive surgery 4 to 6 weeks after completing induction therapy. All patients received preoperative antibiotics and prophylaxis against deep venous thrombosis in the form of sequential compression devices before surgery.

OPERATIVE APPROACHES

Three-field MIE was performed using the technique previously described.^{5,7-11} Thoracoscopic esophageal mobilization with en bloc lymphadenectomy of paraesophageal, subcarinal, and pulmonary ligament nodes was performed through the right side of the chest. This was followed by laparoscopic conduit preparation with en bloc upper abdominal central lymphadenectomy starting at the origin of the left gastric vessels. An end-to-side stapled cervical esophagogastric anastomosis was created using a modified Orringer technique. Open ILE was performed in a similar manner to Dr Lewis' original description with a similar en bloc dissection of lymphatic tissues to that of the MIE.² After laparotomy, gastric mobilization, pyloroplasty, and en bloc lymphadenectomy, the patient was repositioned and a right-sided thoracotomy was performed. The esophagus was mobilized, a gastric tube was made, and a hand-sewn, 2-layer esophagogastric anastomosis was performed.

STATISTICAL ANALYSIS

All collected data were tested for normality and presented as mean (SD) or median and interquartile range (IQR) wherever appropriate or for categorical variables as count and percentage. Univariate analysis of continuous variables was done using the 2-tailed, unpaired *t* test or the Mann-Whitney test, while dichotomous variables were analyzed using the χ^2 test or Fisher exact test as appropriate. Survival was calculated using the Kaplan-Meier method; survival between groups was compared using the log-rank test. Patient demographics, pathology, and perioperative outcomes were used in a multivariate Cox proportional hazards regression model to identify independent predictors of long-term and disease-free survival. The variables used in the Cox proportional hazards regression model were chosen based on their association with survival from established literature. Statistical analysis was performed using R (version 1.10.1; R Development Core Team, Vienna, Austria).

RESULTS

During the study intervals, 33 patients underwent MIE and 31 patients underwent ILE. The comparative demographic, perioperative morbidity, and mortality, data have been previously reported.⁵ To summarize our previous published data, the groups did not differ for age, sex, body mass index, and ASA classification. Although the MIE group had a higher proportion of patients who underwent neoadjuvant chemoradiotherapy (82% [27 of 33 patients]) than the ILE group (65% [20 of 31 patients]), this was not statistically significant ($P = .22$). The proportions of patients with adenocarcinoma and squamous cell carcinoma in both groups were similar ($P = .99$). Clinical staging was not statistically different between the comparative groups ($P = .52$). Mean operative time was longer for patients who underwent MIE compared with those undergoing ILE ($P < .01$). Patients who underwent MIE had less blood lost than patients who underwent ILE ($P < .01$). No significant differences were noted in the mean amount of intravenous fluid used during the 2 procedures ($P = .60$). Median intensive care unit and overall length of hospital stay did not differ between the 2 groups ($P = .10$ and $P = .17$, respectively). Epidural analgesia was commonly used in both groups in the postoperative period ($P = .43$). One patient in the MIE group and 2 in the ILE group had an R1 resection ($P = .35$). Median lymph node harvest was significantly higher in the MIE group compared with the ILE group ($P < .01$). Morbidity and mortality rates did not differ between the 2 groups ($P = .06$ and $P = .34$, respectively).

Table 1 summarizes the univariate analysis of variables that were used in the multivariate Cox proportional hazards regres-

Table 2. Cox Proportional Hazards Regression Model Looking at Independent Predictors of Overall and Disease-Free Survival for Patients With Clinical Stage II and III Esophageal Cancer

Parameter	Hazard Ratio (95% Confidence Interval)
Overall Survival	
Surgical approach: open	0.86 (0.23-3.17)
Neoadjuvant therapy	0.21 (0.04-0.94) ^a
Age	0.95 (0.89-1.02)
Male/sex	63.34 (2.43-1647.0) ^a
Body mass index ^b	0.88 (0.79-0.98) ^a
ASA classifications 3 and 4	4.96 (0.89-27.59)
Pathology	
Complete pathologic response	0.39 (0.04-3.55)
Stage III	16.04 (3.27-78.60) ^a
No. of positive nodes	0.80 (0.58-1.09)
Total lymph node count	0.94 (0.87-1.01)
Presence of postoperative complication	2.79 (0.68-11.51)
Disease-Free Survival	
Age	0.96 (0.90-1.02)
Male sex	21.66 (1.58-297.2) ^a
Body mass index ^b	0.98 (0.91-1.06)
ASA classifications 3 and 4	3.21 (0.59-17.28)
Pathology	
Complete pathologic response	0.50 (0.07-3.31)
Stage III	9.64 (3.26-40.22) ^a
No. of positive nodes	0.82 (0.61-1.10)
Total lymph node count	0.96 (0.91-1.02)
Surgical approach: open	0.74 (0.19-2.90)
Neoadjuvant therapy	0.55 (0.16-1.93)
Presence of postoperative complication	0.90 (0.25-3.25)

Abbreviation: ASA, American Society of Anesthesiologists.

^a $P < .05$.

^bCalculated as weight in kilograms divided by height in meters squared.

sion model. These variables were chosen because they have been demonstrated as predictors of survival by other authors.³⁻⁵ Multivariate Cox proportional hazards regression analysis was used to identify independent predictors of overall and disease-free survival (**Table 2**). Factors that contributed to overall survival included neoadjuvant therapy, male sex, body mass index, and pathologic stage III disease. The only determinants of disease-free survival were male sex and pathologic stage III disease.

The results of the Kaplan-Meier survival analysis are shown in the **Figure**. Median follow-up for the MIE group was 19 months and for the ILE group was 17 months. Overall survival at 2 years was 55% (18 of 33) for the MIE group compared with 32% (10 of 31) for the ILE group (Figure, A). Disease-free survival (survival up to time of recurrence) at 2 years was 55% (18 of 33) for the MIE and 26% (8 of 31) for the ILE groups (Figure, B). Despite the appearance of longer survival in the MIE group, log-rank analysis did not show any statistical differences in disease-free or overall survival between the 2 groups.

COMMENT

The number of reports have been increasing for a single institution experience with MIE since its first description in the early 1990s.² Yet, there remains a scarcity of data comparing the oncologic outcomes on open and minimally invasive approaches. The primary objective of this study was to determine whether 3-field MIE had equivalent oncologic outcomes to that of open ILE. This objec-

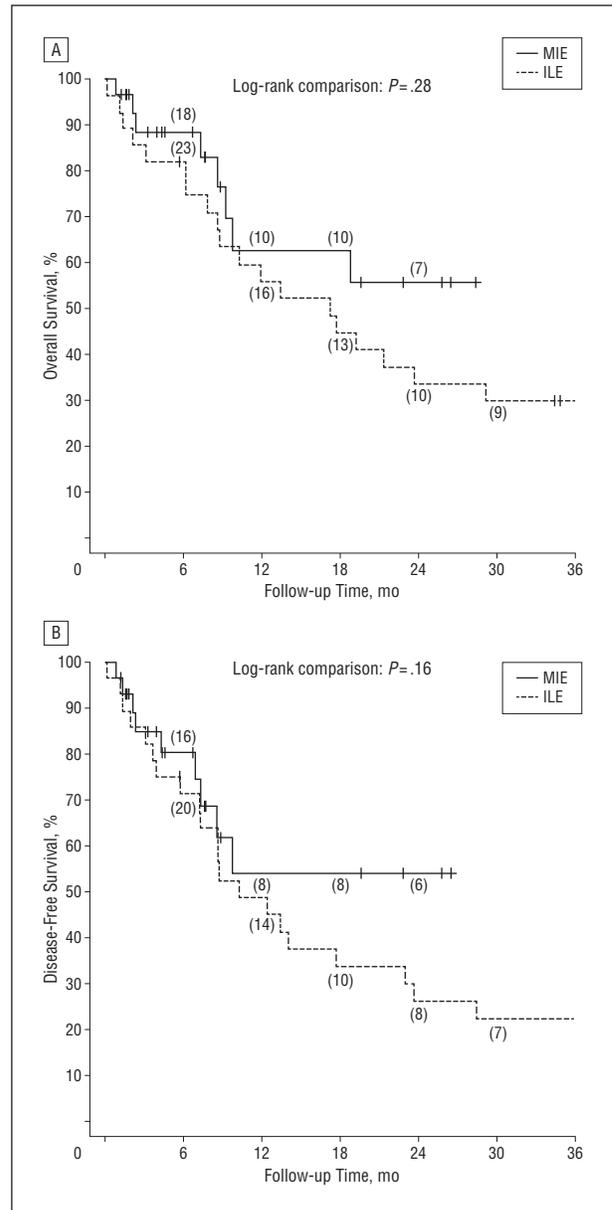


Figure. Kaplan-Meier analysis of overall (A) and disease-free (B) survival in patients who underwent minimally invasive 3-field esophagectomy (MIE) compared with open Ivor Lewis esophagectomy (ILE). Patients at risk are noted in parentheses below the respective curve at selected time points.

tive was examined by performing a comparison of cohorts of patients with clinical stage II or III esophageal cancer who underwent MIE or ILE. Our study showed that patients who underwent MIE had disease-free and overall survival trends that were divergent and favored the MIE group, but this finding was not statistically significant.

In our study, survival curves for MIE and ILE were divergent at 2 years, but patient numbers were insufficient to demonstrate a statistically significant difference. Very few studies have compared MIE and ILE for oncologic outcomes. A series from Australia⁴ comparing 3-field MIE with open ILE reported no significant differences in stage-for-stage survival, but this was confounded by differences in neoadjuvant therapy rates. In a larger comparative cohort study, also from Australia,¹² 56 patients who underwent MIE and 98 patients who underwent open ILE were com-

pared. No differences were noted in survival between the 2 groups.¹² One recent comparative study of 3-field MIE with open ILE also demonstrated no differences in disease-free survival between the 2 groups at the 2-year follow-up.¹³ The findings of our study are consistent with these reports,^{4,12,13} suggesting that MIE and ILE have similar oncologic outcomes and similar survival curves.

Multivariate Cox proportional hazards regression analysis of our data showed that overall survival was poor in male patients and in those with a high body mass index and pathologic stage III disease. However, patients who had neoadjuvant therapy had enhanced survival. These findings are consistent with what has been reported by other investigators.¹⁴⁻¹⁸ However, there were 2 factors that did not significantly affect survival that bear mentioning. In our analysis, complete pathologic response was not a significant predictor of overall survival. This is contrary to what has been reported in 2 recent trials that each contained more than 200 patients.^{16,17} Another factor that did not significantly affect overall survival in our analysis was the number of positive lymph nodes. This runs counter to recent reports using large national databases that have shown that lymph node status significantly affects survival.¹⁹⁻²¹ Similar to overall survival, poor disease-free survival was associated with male sex and pathologic stage III disease. Two recent articles have demonstrated similar findings.^{16,22}

There are important limitations with this study that must be considered. The retrospective design makes it difficult to control for all confounding factors, thus introducing potential bias into the data. Yet, studies similar to this allow for assessment of new techniques and lay the foundation for more robust randomized trials. Although there is a divergence in the survival curves in the early follow-up period, the survival data for our MIE group are still incomplete. A longer follow-up period is still needed to determine overall long-term survival for the MIE group. Finally, while most of the findings of the Cox proportional hazards regression model are consistent with previous articles, they must be tempered by the small sample size used for the analysis.

In conclusion, MIE is comparable to ILE for overall and disease-free oncologic survival for patients with locally advanced esophageal carcinoma. MIE is a safe alternative to ILE, but further studies with longer follow-up are needed to confirm the oncologic results presented.

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