Evidence to Support the Use of Minimally Invasive Esophagectomy for Esophageal Cancer

A Meta-analysis

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Objective: To use meta-analysis to compare oncologic outcomes of minimally invasive esophagectomy (MIE) with open techniques (thoracoscopic and/or laparoscopic). Analysis includes the extent of lymph node (LN) clearance, number of LNs retrieved, staging, geographic variance, and mortality.

Data Sources: A systematic review of the literature was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines using MEDLINE, PubMed, EMBASE, and the Cochrane databases (1950-2012). We evaluated all comparative studies.

Study Selection: All eligible published studies with adequate oncologic data comparing MIE with open resection for carcinoma of the esophagus or esophagogastric junction.

Data Extraction: Two investigators independently selected studies for inclusion and exclusion by article abstraction and quality assessment.

Data Synthesis: After careful review, we included 16 case-control studies with 1212 patients undergoing esophagectomy. The median (range) number of LNs found in the MIE and open groups were 16 (5.7-33.9) and 10 (3.0-32.8), respectively, with a significant difference favoring MIE ($P = .04$). In comparing LN retrieval in Eastern vs Western studies, we found a significant difference in Western centers favoring MIE ($P < .001$). No statistical significance in pathologic staging was found between the open and MIE groups. Generally, no statistically significant difference was found between the open and MIE groups for survival within each time interval (30 days and 1, 2, 3, and 5 years), although the difference favored the MIE group. In comparing survival outcomes in Eastern vs Western centers, a nonsignificant survival advantage (across all time intervals) was found for MIE in the Eastern ($P = .28$) and Western ($P = .44$) centers.

Conclusions: Minimally invasive esophagectomy is a viable alternative to open techniques. Meta-analytic evidence finds equivalent oncologic outcomes to conventional open esophagectomy.

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THE INCIDENCE OF CANCER of the esophagus has increased more rapidly than that of any other solid organ tumor.[1] Despite this, surgery remains the key component in the multimodality treatment of cancer of the esophagus. During the past 30 years, since the inception of minimally invasive surgical techniques, the development of minimally invasive esophagectomy (MIE) as an alternative to open techniques has advanced to improve patient postoperative morbidity and mortality.

See Invited Critique at end of article

Despite the length of time since the first MIE was performed by Cuschieri et al,[2] debate continues as to the safety, efficacy, and oncologic benefit of MIE techniques.[3-6] An important consideration not directly addressed in the existing published meta-analyses and systematic reviews is the comparison of oncologic outcomes of MIE with those of open techniques. The extent of lymphadenectomy and the optimum level of dissection required to optimize patient long-term survival rates and rates of recurrence remain controversial.[7-9] Furthermore, studies on the survival benefits of MIE on a year-to-year basis are lacking. Apparent variations in surgical technique exist between Eastern and Western surgical centers; whether these differences result in dissimilar oncologic outcomes is unknown.

The aims of this study were to (1) compare MIE and open techniques with respect to oncologic outcomes through

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analysis of the number of lymph nodes (LNs) retrieved, oncologic staging, and survival and (2) make comparative observations regarding oncologic outcomes of MIE in Eastern and Western countries.

METHODS

DATA SOURCES

A thorough literature review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines was conducted until May 27, 2012, using MEDLINE (PubMed), EMBASE, and the Cochrane Collaboration and using various combinations of the following terms: **esophagectomy*, *MIE*, *laparasc**, *thoracosc**, *VATS*, *minimally invasive*, *adenocarcinoma*, *squamous cell carcinoma*, *Ivor Lewis*, and *transhiatal* (use of an asterisk in the search phrase denotes truncation). On identifying suitable articles by title, we read the abstracts of these studies to determine eligibility. We retrieved the full article when the article appeared to meet the eligibility criteria. We conducted further cross-referencing of the bibliographies of relevant articles to improve the completeness of this review.

SURGICAL DEFINITIONS

Techniques for MIE vary considerably between countries and centers. In general, the following 3 open techniques are commonly used: (1) Ivor Lewis, defined as gastric mobilization via laparotomy with esophageal and nodal dissection via right-sided thoracotomy and an intrathoracic anastomosis; (2) modified McKeown or 3-stage esophagectomy, defined as gastric mobilization via laparotomy with esophageal and nodal dissection via right-sided thoracotomy and cervical anastomosis via a neck incision; and (3) transhiatal, defined as gastric mobilization by laparotomy, distal esophageal, and mediastinal LN dissection through the diaphragmatic hiatus with proximal esophageal mobilization and a cervical anastomosis via a neck incision.

In this study, surgical techniques were classified as MIE only if abdominal and thoracic stages were laparoscopic or thoracoscopic with or without hand assistance. For transhiatal esophagectomy to be an MIE, the abdominal operation was conducted laparoscopically or via hand-assisted laparoscopy. This latter category included laparoscopic inversion esophagectomy, which uses an esophageal inversion by means of a vein stripper with a cervical anastomosis via a neck incision.

STUDY SELECTION CRITERIA

We included all published full-text English-language studies comparing MIE with open resection for carcinoma of the esophagus or esophagogastric junction. Inclusion criteria consisted of (1) treatment including MIE, not hybrid MIE; (2) intention to treat; (3) studies of cases of esophageal cancer or Barrett esophagus with high-grade dysplasia; (4) studies comparing outcomes between open and MIE techniques; and (5) studies reporting a minimum set of oncologic data (LNs harvested, survival data, tumor staging, induction therapy, and extent of LN clearance). We excluded publications in non–peer-reviewed journals, review articles without original data, all studies not reporting on a minimal set of oncologic operative outcomes or not comparing MIE with open esophagectomies, case series and case reports without comparison, and studies with overlap between authors with previous published data.

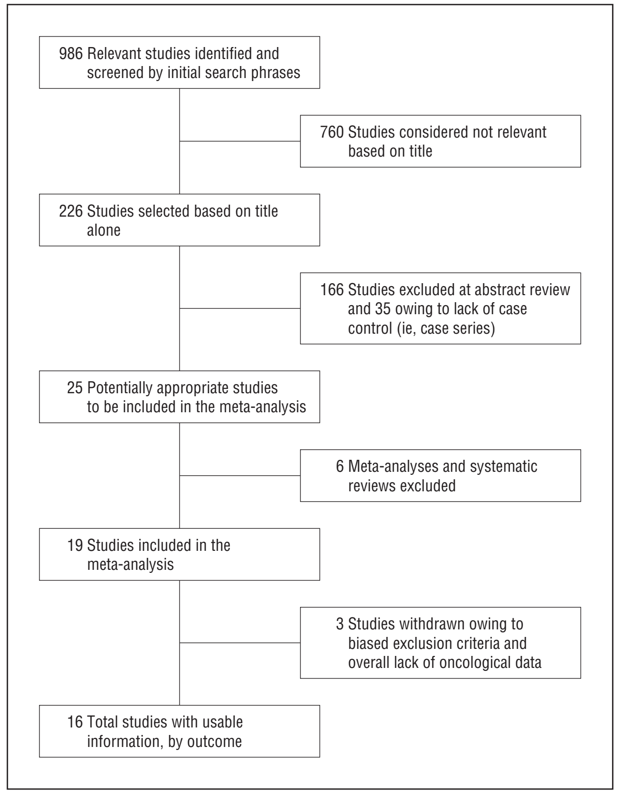

Figure 1. Systematic review search flowchart.

DATA EXTRACTION

Two of us (M.D. and G.D.E.) independently selected studies for inclusion and exclusion. Consensus was reached on studies that were not included or excluded by both authors. All data were entered in a computer database (Microsoft Excel; Mircosoft Corporation) for analysis. We extracted commonly available data across the 16 studies identified. In this case, descriptive statistical comments were made using the studies in which similar data were available. Reporting bias, variations in surgical technique, and variations in the selection criteria of patients between studies were found; hence, comparisons between studies would not provide any useful plausible evidence and therefore were not conducted. We chose to focus specifically on the comparison between MIE and the open technique within each study.

STATISTICAL ANALYSIS

Multiple comparisons between the 2 operative groups involved analyzing the means, medians, and standard deviations for each identified variable where possible. We performed statistical analyses for survival data using the hazard ratio (HR) as the summary statistic until the longest follow-up point. We calculated the HRs from studies using Kaplan-Meier survival when comparing the MIE with the open group. We analyzed continuous variables, such as the number of LNs retrieved and operative variables, using a weighted means difference (WMD) as the summary statistic. We used a random-effects model to account for the significant levels of heterogeneity in surgical techniques in other various centers. Heterogeneity was assessed using the I^2 statistic. Funnel plots were created to evaluate the presence of publication bias. Also, we used the Egger weighted regression test to determine statistically significant publication bias. Differences in *P* values of less than .05 were considered statistically significant.

Table 1. Overall Characteristics of the Studies

Source	Country	Sample Size, No. of Patients	Sex, %: MIE Group Male	MIE Group Female	Open Group Male	Open Group Female	Mean Age, y	Specific MIE Technique Used	EOL, No. of Fields
Schoppmann et al,[16] 2010	Austria	62	25	6	21	10	60.1	TLSE	2
Smithers et al,[17] 2007	Australia	446	20	3	104	10	62.5	TLSE	2
Fabian et al,[18] 2008	United States	65	16	6	31	12	62.0	TLSE	2
Shiraishi et al,[9] 2006	Japan	153	62	16	31	6	62.4	TLSE	3
Bresadola et al,[19] 2006	Italy	28	8	6	13	1	60.24	THE + TLSE	2
Kunisaki et al,[7] 2004	Japan	45	21	9	12	3	62.5	VATS + HALS	2
Van den Broek et al,[20] 2004	The Netherlands	45	19	6	14	6	63.5	THE	2
Osugi et al,[21] 2003	Japan	119	34	13	57	15	63.7	VATS	3
Zingg et al,[22] 2009	Australia	154	45	11	71	27	67.05	TLSE	2
Taguchi et al,[23] 2003	Japan	69	20	20	24	5	61.65	VATS	3
Law et al,[24] 1997	Hong Kong	81	13	5	55	8	64.5	TSE	2
Pham et al,[25] 2010	United States	90	41	3	33	13	61.5	TLSE	2
Parameswaran et al,[15] 2009	United Kingdom	80	45	3	21	9	67.5	TLSE	2
Nguyen et al,[26] 2000	United States	54	7	5	29	7	65.3	TLSE	2
Perry et al,[27] 2009	United States	42	18	11	17	4	65.4	LIE	2
Bernabe et al,[28] 2005	United States	31	11	3	16	1	64.0	THE	2

Abbreviations: EOL, extent of lymphadenectomy; HALS, hand-assisted laparoscopic esophagectomy; LIE, laparoscopic inversion esophagectomy; MIE, minimally invasive esophagectomy; THE, transhiatal esophagectomy; TLSE, thoracolaparoscopic esophagectomy; TSE, thoracoscopic-assisted esophagectomy; VATS, video-assisted thoracoscopic esophagectomy.

RESULTS

An initial search identified 226 studies, of which 201 were rejected at abstract review because they did not meet the specified inclusion criteria (**Figure 1**). From 1997 to 2011, 60 articles related to MIE for cancer consisted of case series (n=35), case-control studies (n=19), systematic reviews (n=3), or meta-analyses (n=3). The 3 meta-analyses published from 2009 through 2010 included 8 to 12 retrospective case-matched studies.[10-12] Among the 35 case series on MIE, the largest included a total of 222 patients.[13] The data within the studies in the meta-analyses and systematic reviews had a strong emphasis on perioperative mortality and morbidity outcomes.[6,10-12,14,15] The remaining 19 studies were all retrospective case-control studies. We did not include 3 case-control studies owing to exclusion of advanced-stage disease and a lack of overall oncologic data. The other 16 studies were included in this meta-analysis. The overall characteristics of the included studies are shown in **Table 1**. Comparison between the open and MIE groups was possible with the data available for direct comparison. Most of the studies originated from Western countries (n=11); the remainder, from Eastern countries (n=5)

In total, this study included 1212 patients undergoing esophagectomy (718 [59.2%] using the open technique and 494 [40.8%] using MIE). In the open group, the most common technique was a transthoracic (Ivor Lewis or modified McKeown) approach (76.3%). Transhiatal approaches constituted 23.7% of all patients undergoing open esophagectomy. Within the MIE group, the most common technique used a transthoracic thoracoscopic (including video-assisted) and laparoscopic approach (53.4%). Laparoscopic approaches included hand assisted, transhiatal, and, in a single study, a laparoscopic inversion esophagectomy.

Esophageal cancer types were grouped into the following 3 main types: (1) squamous cell carcinoma, (2) adenocarcinoma, and (3) high-grade dysplasia/carcinoma in situ. Proportions of cancer types in the MIE group compared with the open group were similar (MIE group: 39.8% adenocarcinoma, 52.1% squamous cell carcinoma, and 8.1% high-grade dysplasia/carcinoma in situ; open group: 37.7% adenocarcinoma, 54.2% squamous cell carcinoma, and 8.1% high-grade dysplasia/carcinoma in situ).

ONCOLOGIC OUTCOMES

The overall extent of LN retrieval varied between studies (**Table 2**). The largest study showed no statistical significance with respect to lymphadenectomy between the open and MIE groups ($P=.76$).[17] The range of LNs dissected varied from a median of as few as 3 to as many as 33.9. Lymph node clearance in 4 studies was greater in the MIE group than in the open group ($P<.001$).[15,18,25,27] One study showed a lesser LN yield in the MIE group compared with the open group[24] ($P=.01$); the authors had stated that MIE at the time was in its early phases and that the extent of lymphadenectomy was not easily replicated compared with open esophagectomy. Overall, the median (range) number of LNs found in the open and MIE groups was 10 (3.0-32.8) and 16 (5.7-33.9), of which there was a significant overall difference between the open and MIE groups (WMD, 0.371 [95% CI, −0.049 to 0.693; $P=.02$). Analytic data using a WMD, random-effects model for the overall number of LNs dissected is shown in

Table 2. Number of LNs Retrieved: Comparison of Open vs MIE Procedures

Source	Sample Size, No. of Patients	Reported No. of LNs Retrieved[a]		*P* Value[b]
		MIE Group	Open Group	
Schoppmann et al,[16] 2010	62	17.9 (7.7)	20.5 (12.6)	.33
Smithers et al,[17] 2007	446	17 (9-33)	16 (1-44)	.76
Fabian et al,[18] 2008	65	15 (6)	8 (7)	<.001
Bresadola et al,[19] 2006	28	22.23 (12.0)	18.61 (3.4)	.45
Kunisaki et al,[7] 2004	45	24.5 (10)	26.6 (10.4)	.51
Van den Broek et al,[20] 2004	45	7 (4.9)	6.5 (4.9)	.73
Osugi et al,[21] 2003	119	33.9 (12)[c]	32.8 (14)[c]	.61
Zingg et al,[22] 2009	154	5.7 (0.4)[c]	6.75 (0.5)[c]	.15
Taguchi et al,[23] 2003	69	31.9 (11.5)	29.3 (10.1)	.32
Law et al,[24] 1997	81	7 (2-13)	13 (5-34)	.01
Pham et al,[25] 2010	90	13 (9-15)	8 (3-14)	<.001
Parameswaran et al,[15] 2009	80	23 (7-49)	10 (2-23)	<.001
Nguyen et al,[26] 2000	54	10.8 (8.4)	6.6 (5.8)	.06
Perry et al,[27] 2009	42	10 (4-12)	3 (0-7)	<.001
Bernabe et al,[28] 2005	31	9.8	8.7	.31

Abbreviations: LNs, lymph nodes; MIE, minimally invasive esophagectomy.
[a] Data are presented as median (SE) or median (range).
[b] $P < .05$ considered statistically significant.
[c] Data are given as median (SD).

Source	Statistics for Each Study: Std Diff, Mean	SE	(95% CI)	*P* Value
Schoppmann et al,[16] 2010	−0.25	0.25	(−0.75 to 0.25)	.33
Smithers et al,[17] 2007	0.07	0.23	(−0.38 to 0.52)	.76
Fabian et al,[18] 2008	1.10	0.28	(0.55 to 1.65)	.00
Bresadola et al,[19] 2006	0.28	0.38	(−0.46 to 1.03)	.45
Kunisaki et al,[7] 2004	−0.21	0.32	(−0.83 to 0.41)	.51
Van den Broek et al,[20] 2004	0.10	0.30	(−0.49 to 0.69)	.73
Osugi et al,[21] 2003	0.08	0.16	(−0.24 to 0.41)	.61
Zingg et al,[22] 2009	−0.24	0.17	(−0.57 to 0.09)	.15
Taguchi et al,[23] 2003	0.28	0.28	(−0.28 to 0.84)	.32
Law et al,[24] 1997	−0.71	0.27	(−1.24 to −0.17)	.01
Pham et al,[25] 2010	1.14	0.23	(0.69 to 1.58)	<.001
Parameswaran et al,[15] 2009	0.73	0.24	(0.26 to 1.20)	<.001
Nguyen et al,[26] 2000	0.55	0.29	(−0.03 to 1.12)	.06
Perry et al,[27] 2009	1.86	0.37	(1.14 to 2.59)	<.001
Bernabe et al,[28] 2005	0.37	0.36	(−0.35 to 1.08)	.31
	0.33	0.16	(0.02 to 0.63)	.04

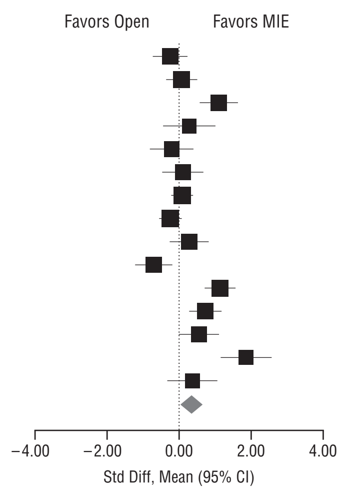

Figure 2. Forest plot for lymph nodes retrieved, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. Std Diff indicates standard difference.

Figure 2. Funnel plots and Egger regression analysis for the number of LNs retrieved and survival showed no significant publication bias (**Figure 3**A and B) ($P=.53$ and $P=.14$, respectively).

The pathologic stage of cancers within each operative group is shown in **Table 3**. One study used hybrid MIE, in which the abdominal phase was conducted via an open approach.[17] Nine studies published TNM staging data; 6, International Union Against Cancer staging data; and 1, no staging data. In 1 study, a statistically significant difference was found in the proportion of patients with stage III cancer between the open (65.8%) and MIE (52.1%) groups ($P=.03$).[17] Overall, no statistically significant difference was found in pathologic staging between the open and MIE groups. Patients in the MIE group used significantly more neoadjuvant treatment (54.9%) compared with the open group (34.7%) ($P<.001$). Some studies did not provide adequate data, whereas some used qualitative data to represent their cases.

Cumulative survival data were published in most of the included studies. Ten (63%) and eleven (66%) studies had published survival data for the open and MIE groups, respectively; however, not all of these studies stated data for each time interval. Generally, good short-term (30-day) survival rates were found in both groups. Results of the meta-analyses for survival by stage interval are shown in **Figures 4**, **5**, **6**, **7**, and **8**. Survival differences expressed by HRs for the specified time intervals were statistically nonsignificant ($P > .05$). A trend for survival favored MIE for all time intervals, although this difference was statistically nonsignificant.

All intervals were found to be nonheterogeneous, including the 30-day ($I^2 < 0.001$ [$P = .39$]), 1-year ($I^2 < 0.001$ [$P = .74$]), 2-year ($I^2 < 0.0001$ [$P = .74$]), 3-year ($I^2 < 0.001$ [$P = .78$]), and 5-year ($I^2 < 0.001$ [$P = .65$]) intervals. Combined survival for all studies (**Figure 9**) favored MIE, but the difference was statistically nonsignificant (HR, 0.87 [95% CI, −0.70 to 1.08]; $P = .22$) (for heterogeneity, $I^2 < 0.001$ [$P = .81$]).

Operative variables were collated from the 16 studies comparing open vs MIE groups. Overall, the median (range) length of hospital stay was 18.3 (10.0-32.7) and 14.6 (9.1-29.6) days for the open and MIE groups, respectively ($P = .16$). The overall median (range) length of each operative procedure was 328 (178-487) and 341 (221-469) minutes for the open and MIE groups, respectively ($P = .71$). Statistically, the lengths of the hospital stay and the operative procedure were not significantly different between the open and MIE groups.

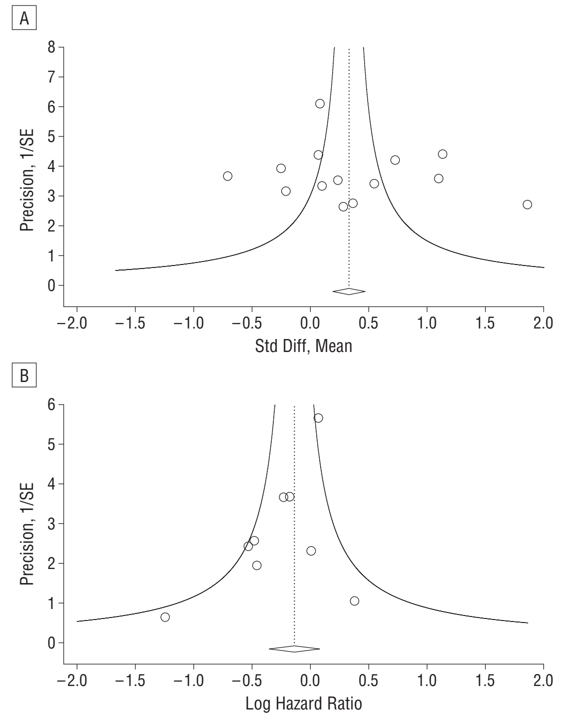

Figure 3. Funnel plot for publication bias of lymph node retrieval (A) and survival (B). Open circles indicate studies in the meta-analysis; open diamonds, the mean effect size; and curves, the 95% CI for the meta-analysis. Std Diff indicates standard difference.

EAST VS WEST

Oncologic data collated were assigned to the Eastern or Western group. Surgical procedures conducted in Eastern countries (mainly Japan) were allocated to the East, whereas surgical procedures conducted in Western countries (the United States, Australia, and Europe) were allocated to the West.

Survival data for East vs West were available in 6 and 3 studies, respectively. Meta-analytic data are shown in **Figure 10**. In the Eastern group, the difference between open and MIE techniques was found to

Table 3. Tumor Stage of Patients Treated by Esophagectomy: Comparison of MIE vs Open/HMIE Procedures

	Procedure, % of Patients			P Value[a]	
TMN Stage	MIE (n = 268) (9 Studies)	Open (n = 452) (9 Studies)	HMIE (n = 309) (1 Study)	MIE vs Open	MIE vs HMIE
0, HGD or benign	3.8	2.3	7.2	.25	NA
I	17.0	12.5	22.6	.21	NA
IIa	23.3	23.9	17.9	.91	NA
IIb	12.3	14.5	15.1	.52	NA
III	42.9	42.0	34.4	.82	NA
IV	2.0	4.1	2.8	.14	NA
UICC Stage	**MIE (n = 171) (5 Studies)**	**Open (n = 162) (6 Studies)**	**HMIE (n = 13) (1 Study)**	**MIE vs Open**	**MIE vs HMIE**
0	18.2	15.1	15.4	.50	NA
I	39.0	27.6	0	.11	NA
IIa	14.3	12.3	15.4	.26	NA
IIb	15.8	11.1	23.1	.82	NA
III	9.2	17.3	46.2	.27	NA
	MIE (n = 307) (8 Studies)	**Open (n = 547) (7 Studies)**	**HMIE (n = 360) (1 Study)**	**MIE vs Open**	**MIE vs HMIE**
Neoadjuvant therapy	54.9	34.7	43.8	<.001	.25

Abbreviations: HGD, high-grade dysplasia; HMIE, hybrid minimally invasive esophagectomy (MIE); NA, not applicable because not calculable; UICC, International Union Against Cancer.
[a] $P < .05$ considered statistically significant.

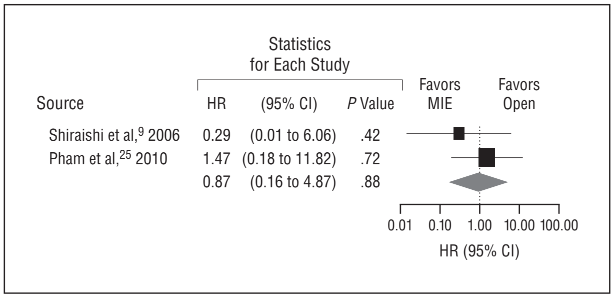

Figure 4. Forest plot for 30-day survival, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

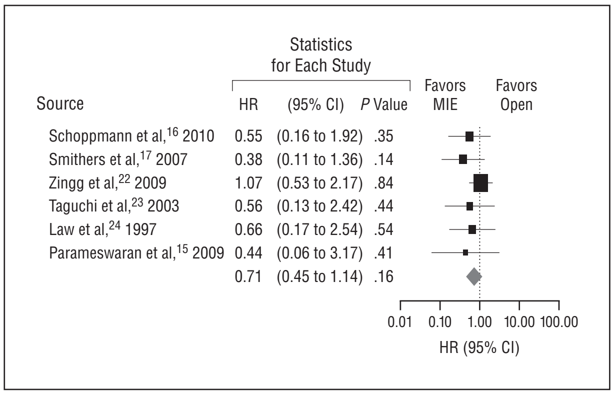

Figure 5. Forest plot for 1-year survival, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

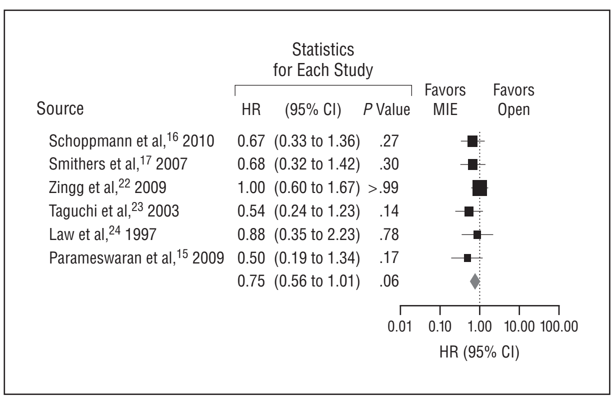

Figure 6. Forest plot for 2-year survival, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

be nonsignificant, favoring MIE overall (HR, 0.80 [95% CI, 0.54-1.20; $P=.28$]) with no heterogeneity ($I^2<0.0001$ [$P=.82$]). The Western group showed similar results, with nonsignificant differences favoring MIE (HR, 0.90 [95% CI, 0.70-1.17]; $P=.44$) with no heterogeneity ($I^2<0.0001$ [$P=.51$]).

Comparison of East vs West with regard to the number of LNs retrieved is shown in **Figure 11**. Four studies constituting the Eastern group resulted in nonsignificant differences between open and MIE procedures

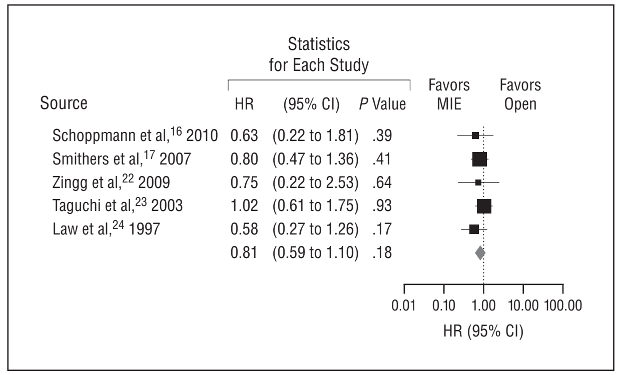

Figure 7. Forest plot for 3-year survival, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

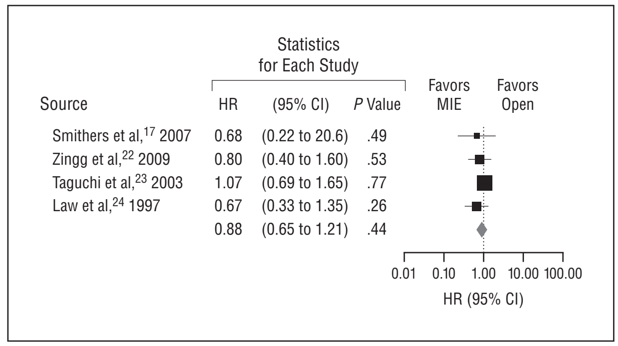

Figure 8. Forest plot for 5-year survival, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

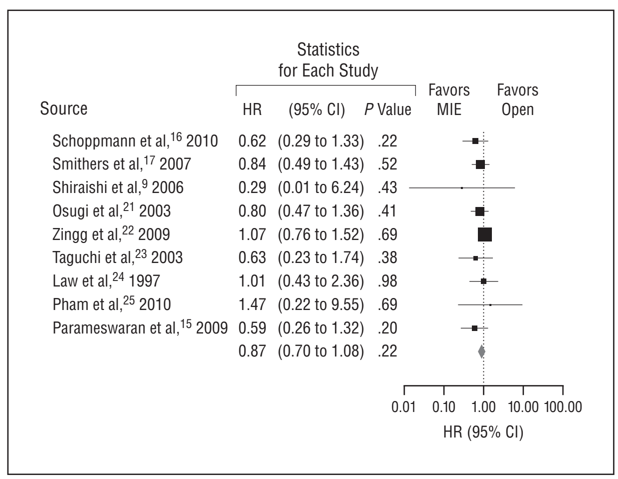

Figure 9. Forest plot for survival for individual studies, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

(WMD, −0.12 [95% CI, −0.52 to 0.29]; $P=.56$) with heterogeneity ($I^2=-62.60$ [$P=.046$]). The Western group consisted of 11 studies, resulting in significant differences between open and MIE procedures and favoring MIE (WMD, 0.50 [95% CI, 0.12-0.88; $P=.01$]) with heterogeneity ($I^2=-82.97$ [$P<.001$]).

Group by Region	Source	HR	(95% CI)	*P* Value
East	Shiraishi et al,[9] 2006	0.29	(0.01 to 6.24)	.43
East	Osugi et al,[21] 2003	0.80	(0.47 to 1.36)	.41
East	Taguchi et al,[23] 2003	0.63	(0.23 to 1.74)	.38
East	Law et al,[24] 1997	1.01	(0.43 to 2.36)	.98
East		0.80	(0.54 to 1.20)	.28
West	Schoppmann et al,[16] 2010	0.62	(0.29 to 1.33)	.22
West	Smithers et al,[17] 2007	0.84	(0.49 to 1.43)	.52
West	Zingg et al,[22] 2009	1.07	(0.76 to 1.52)	.69
West	Pham et al,[25] 2010	1.47	(0.22 to 9.55)	.69
West	Parameswaran et al,[15] 2009	0.59	(0.26 to 1.32)	.20
West		0.90	(0.70 to 1.17)	.44

(Statistics for Each Study)

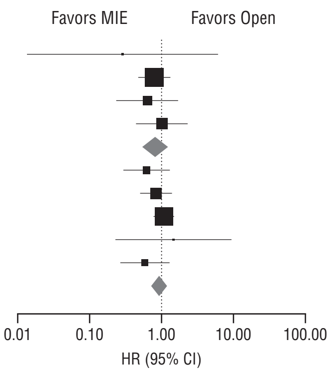

Figure 10. Forest plot for survival, East vs West, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. HR indicates hazard ratio.

Group by Region	Source	Std Diff, Mean	SE	(95% CI)	*P* Value
East	Kunisaki et al,[7] 2004	−0.21	0.32	(−0.83 to 0.41)	.51
East	Osugi et al,[21] 2003	0.08	0.16	(−0.24 to 0.41)	.61
East	Taguchi et al,[23] 2003	0.28	0.28	(−0.28 to 0.84)	.32
East	Law et al,[24] 1997	−0.71	0.27	(−1.24 to −0.17)	.01
East		−0.12	0.21	(−0.52 to 0.29)	.56
West	Schoppmann et al,[16] 2010	−0.25	0.25	(−0.75 to 0.25)	.33
West	Smithers et al,[17] 2007	0.07	0.23	(−0.38 to 0.52)	.76
West	Fabian et al,[18] 2008	1.10	0.28	(0.55 to 1.65)	<.001
West	Bresadola et al,[19] 2006	0.28	0.38	(−0.46 to 1.03)	.45
West	Van den Broek et al,[20] 2004	0.10	0.30	(−0.49 to 0.69)	.73
West	Zingg et al,[22] 2009	−0.24	0.17	(−0.57 to 0.09)	.15
West	Pham et al,[25] 2010	1.14	0.23	(0.69 to 1.58)	<.001
West	Parameswaran et al,[15] 2009	0.73	0.24	(0.26 to 1.20)	<.001
West	Nguyen et al,[26] 2000	0.55	0.29	(−0.03 to 1.12)	.06
West	Perry et al,[27] 2009	1.86	0.37	(1.14 to 2.59)	<.001
West	Bernabe et al,[28] 2005	0.37	0.36	(−0.35 to 1.08)	.31
West		0.50	0.19	(0.12 to 0.88)	.01

(Statistics for Each Study)

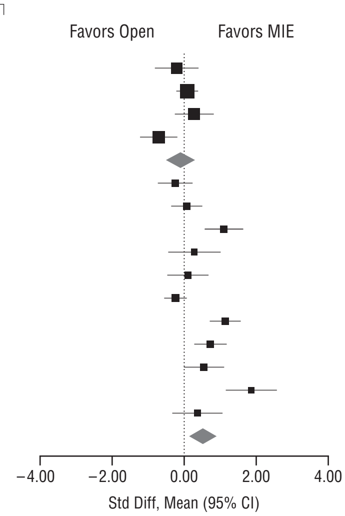

Figure 11. Forest plot for overall lymph nodes retrieved, East vs West, open vs minimally invasive esophagectomy (MIE). The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random effects models. Std Diff indicates standard difference.

COMMENT

Numerous case series on MIE were published before 2011, but no randomized controlled trials have compared open and MIE groups with respect to short-term outcomes or oncologic impact. We used retrospective case-controlled studies to improve the validity of current clinical evidence. We included 16 case-control studies, the largest of which was by Smithers and colleagues[17] with a total of 446 cases (309 hybrid MIE, 23 MIE, and 114 open). In their study, elimination of study bias was difficult. Each study presents its own limitations, such as small case numbers, surgical bias with inconsistency among the surgeons, exclusion of certain stages of cancers, inconsistencies in follow-up, and variances in operative technique and patient selection criteria. We recognize the limitations of this study when analyzing data from retrospective studies that show potential heterogeneity without addressing explicit confounding variables.

LYMPHADENECTOMY

Our study has shown that, despite the level of heterogeneity between studies, the difference in LN retrieval was statistically significant, favoring MIE in 5 studies and overall by meta-analysis. Criticisms of MIE techniques with regard to poor LN yield are valid in the setting of a center recently adopting MIE techniques and having a distinct learning curve from other centers. Individual authors have purported to improve visualization of LN by thoracoscopic means. Overall, our findings show an increased number of LNs resected via MIE (median [range], 16 [5.7-33.9]) vs open procedures (10 [3.0-32.8]). However, the drawback of using LN numbers as a surrogate for extent of lymphadenectomy is that the numbers of

LNs examined and reported are determined by the surgical protocol and quality of pathological examination.

As shown in Table 1, LN clearance varies between studies because of the choice of operative technique and extent of lymphadenectomy. An apparent observation is a greater-than-average LN yield in the Japanese studies, where surgeons consistently perform 2-field extended or 3-field lymphadenectomy. In the comparison between East and West, the number of LNs dissected was nonsignificant in Eastern countries (open vs MIE) but significant in Western countries ($P < .001$). Thus, we demonstrated that an extensive LN clearance is possible with MIE techniques. In Japanese centers, MIE has been more widely adapted, and the operative technique has matured to a greater extent than in the West. Despite the variance in LN yield between studies, overall it can be concluded that surgeons performing MIE have a similar or greater capability for lymphadenectomy compared with those using standard open techniques.

Tumor types (adenocarcinoma or squamous cell carcinoma) within each study were fairly similar (Table 3). Overall, the distribution of patients in each stage was similar; however, tumor staging in some larger studies had a higher proportion of early-stage disease in the MIE group, and the open group tended to have a larger proportion of patients with advanced-stage disease.[17-19]

ONCOLOGIC OUTCOMES

The comparison of survival data between studies revealed no significant survival advantage based on time intervals. The analysis for survival comparing open and MIE procedures between studies showed no statistically significant survival advantage for either technique (HR, 0.87 [$P = .22$]) with no heterogeneity ($I^2 < 0.001$ [$P = .81$]).

In comparing East vs West, we found that the difference in survival was also statistically nonsignificant, favoring MIE in the East (HR, 0.80 [$P = .28$]), with similar findings in the West (HR, 0.90 [$P = .44$]), with both groups showing no heterogeneity for these findings. In this case, the studies included in the analysis for the Eastern group were fairly similar with respect to tumor staging and type; however, data on the use of chemoradiation therapy were lacking and may be a confounding factor in this result.

In our study, most of the patients in the MIE group (54.9%) underwent induction therapy as opposed to the open group (34.7%). The reasons for this difference may vary between centers. Generally, the indication for pretreatment may have been more liberally applied in patients for whom preoperative staging was not confirmed and an MIE was planned and for whom surgeons may have applied differing criteria for selecting patients for induction therapy.

With regard to the quality of evidence, the 16 studies had significant but explicable heterogeneity in a number of variables (mostly LN retrieval); however, no evidence of publication bias was found with respect to this variable, and a meta-regression could not be attempted because of the relatively low number of studies for each group. Restricting results to the English language could have affected publication bias during the review process.

CONCLUSIONS

This review focuses on the oncologic merits of MIE techniques compared with conventional open techniques. In the analysis of the data procured from 16 separate case-control studies, the capability of surgeons to perform an adequate lymphadenectomy using MIE is achieved. Evidence points to the capacity of MIE techniques for greater LN yield owing to better visualization of the operative field. In addition, we find no statistically significant difference in survival rates between open procedures and MIE. In comparing East vs West, Western centers had a statistically better LN yield with open vs MIE, but the difference is not significant in Eastern centers. On survival, Eastern and Western centers showed no statistically significant survival advantage for MIE. Finally, although a lack of standardized and controlled data limits the methods used in this study, the evidence suggests that the use of MIE is no better or worse in achieving similar oncologic outcomes than are open techniques. Further randomized controlled studies are needed to provide credible clinical evidence of the oncologic outcomes of open techniques vs MIE.

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REFERENCES

1. Shah R, Jobe BA. Open versus minimally invasive esophagectomy: what is the best approach? minimally invasive esophagectomy. *J Gastrointest Surg*. 2011;15(9):1503-1505.
2. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. *J R Coll Surg Edinb*. 1992;37(1):7-11.
3. Gemmill EH, McCulloch P. Systematic review of minimally invasive resection for gastro-oesophageal cancer. *Br J Surg*. 2007;94(12):1461-1467.
4. Law S. Optimal surgical approach for esophagectomy: the debate still goes on? *Ann Thorac Cardiovasc Surg*. 2009;15(5):277-279.
5. Smithers BM. Minimally invasive esophagectomy: an overview. *Expert Rev Gastroenterol Hepatol*. 2010;4(1):91-99.
6. Verhage RJ, Hazebroek EJ, Boone J, Van Hillegersberg R. Minimally invasive surgery compared to open procedures in esophagectomy for cancer: a systematic review of the literature. *Minerva Chir*. 2009;64(2):135-146.
7. Kunisaki C, Hatori S, Imada T, et al. Video-assisted thoracoscopic esophagectomy with a voice-controlled robot: the AESOP system. *Surg Laparosc Endosc Percutan Tech*. 2004;14(6):323-327.

8. Law S, Wong J. Lymph node dissection in surgical treatment of esophageal neoplasms. *Surg Oncol Clin N Am.* 2007;16(1):115-131.
9. Shiraishi T, Kawahara K, Shirakusa T, Yamamoto S, Maekawa T. Risk analysis in resection of thoracic esophageal cancer in the era of endoscopic surgery. *Ann Thorac Surg.* 2006;81(3):1083-1089.
10. Biere SS, Cuesta MA, van der Peet DL. Minimally invasive versus open esophagectomy for cancer: a systematic review and meta-analysis. *Minerva Chir.* 2009;64(2):121-133.
11. Nagpal K, Ahmed K, Vats A, et al. Is minimally invasive surgery beneficial in the management of esophageal cancer? a meta-analysis. *Surg Endosc.* 2010;24(7):1621-1629.
12. Sgourakis G, Gockel I, Radtke A, et al. Minimally invasive versus open esophagectomy: meta-analysis of outcomes. *Dig Dis Sci.* 2010;55(11):3031-3040.
13. Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al. Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg.* 2003;238(4):486-495.
14. Biere SS, van der Peet DL, Cuesta MA. Minimally invasive esophagectomy. *Ann Surg.* 2010;251(1):178-179.
15. Parameswaran R, Veeramootoo D, Krishnadas R, Cooper M, Berrisford R, Wajed S. Comparative experience of open and minimally invasive esophagogastric resection. *World J Surg.* 2009;33(9):1868-1875.
16. Schoppmann S, Prager G, Langer F, et al. Open versus minimally invasive esophagectomy: a single-center case controlled study. *Surg Endosc.* 2010;24(12):3044-3053.
17. Smithers BM, Gotley DC, Martin I, Thomas JM. Comparison of the outcomes between open and minimally invasive esophagectomy. *Ann Surg.* 2007;245(2):232-240.
18. Fabian T, Martin JT, McKelvey AA, Federico JA. Minimally invasive esophagectomy: a teaching hospital's first year experience. *Dis Esophagus.* 2008;21(3):220-225.
19. Bresadola V, Terrosu G, Cojutti A, Benzoni E, Baracchini E, Bresadola F. Laparoscopic versus open gastroplasty in esophagectomy for esophageal cancer: a comparative study. *Surg Laparosc Endosc Percutan Tech.* 2006;16(2):63-67.
20. Van den Broek WT, Makay Ö, Berends FJ, et al. Laparoscopically assisted transhiatal resection for malignancies of the distal esophagus. *Surg Endosc.* 2004;18(5):812-817.
21. Osugi H, Takemura M, Higashino M, Takada N, Lee S, Kinoshita H. A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. *Br J Surg.* 2003;90(1):108-113.
22. Zingg U, McQuinn A, DiValentino D, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. *Ann Thorac Surg.* 2009;87(3):911-919.
23. Taguchi S, Osugi H, Higashino M, et al. Comparison of three-field esophagectomy for esophageal cancer incorporating open or thoracoscopic thoracotomy. *Surg Endosc.* 2003;17(9):1445-1450.
24. Law S, Fok M, Chu KM, Wong J. Thoracoscopic esophagectomy for esophageal cancer. *Surgery.* 1997;122(1):8-14.
25. Pham TH, Perry KA, Dolan JP, et al. Comparison of perioperative outcomes after combined thoracoscopic-laparoscopic esophagectomy and open Ivor-Lewis esophagectomy. *Am J Surg.* 2010;199(5):594-598.
26. Nguyen NT, Follette DM, Wolfe BM, Schneider PD, Roberts P, Goodnight JE Jr. Comparison of minimally invasive esophagectomy with transthoracic and transhiatal esophagectomy. *Arch Surg.* 2000;135(8):920-925.
27. Perry KA, Enestvedt CK, Pham T, et al. Comparison of laparoscopic inversion esophagectomy and open transhiatal esophagectomy for high-grade dysplasia and stage I esophageal adenocarcinoma. *Arch Surg.* 2009;144(7):679-684.
28. Bernabe KQ, Bolton JS, Richardson WS. Laparoscopic hand-assisted versus open transhiatal esophagectomy: a case-control study. *Surg Endosc.* 2005;19(3):334-337.

INVITED CRITIQUE

The Goal of Esophagogastrectomy for Patients With Esophageal Cancer

Minimally Invasive or Maximally Effective?

Dantoc et al[1] performed a meta-analysis of 16 studies that included 1212 patients undergoing esophagectomy for esophageal cancer. The authors found that the median number of lymph nodes removed was higher in the group undergoing minimally invasive esophagectomy (MIE) compared with the open group (16 vs 10 [$P = .04$]), but they found no difference in 30-day or overall survival. From this analysis, the authors concluded that MIE is a viable alternative to open esophagectomy with equivalent oncological outcomes.

The authors should be commended for their work to assess the effectiveness of MIE in patients with esophageal cancer. However, equivalent outcomes between MIE and open esophagectomy may not be the optimal standard for supporting the use of MIE for patients with esophageal cancer. For instance, in the 2 studies included in this meta-analysis that examined 30-day mortality, the rates were 3.9%[2] and 5.6%,[3] respectively. These rates are higher than the mortality rate of 2.7% observed in 2315 patients who underwent esophagectomy in 73 centers that participate in the Society of Thoracic Surgeons General Thoracic Database.[4] The study by Dantoc et al[1] does not include the rates of complications that have been shown to affect short- and long-term outcomes negatively after esophagogastrectomy.[5]

Surgeons performing esophagectomy for esophageal cancer must direct their efforts toward reducing the rates for operative mortality, anastomotic leak, vocal cord paralysis, and chylothorax to less than 3% for each of these complications while still achieving the oncological result of complete resection with negative margins. The esophagectomy method used, whether open or minimally invasive, must be optimized at each institution to achieve these goals. Using this strategy, esophageal surgeons can provide a "maximally effective esophagectomy" for each of their patients.

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