Open versus hybrid versus totally minimally invasive Ivor Lewis esophagectomy: Systematic review and meta-analysis

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ABSTRACT

Background: Hybrid and minimally invasive approaches have emerged as less invasive alternatives to open Ivor Lewis esophagectomy. The aim of this study was to compare surgical outcomes between open (OE), hybrid (HE), and totally minimally invasive esophagectomy (TMIE).

Methods: A systematic literature search was performed to analyze outcomes after OE, HE, and TMIE with intrathoracic anastomosis. Main outcomes included anastomotic leak rate, overall morbidity, and 30-day mortality. A meta-analysis of proportions was used to assess the effect of each approach on different outcomes.

Results: A total of 130 studies comprising 16,053 patients were included for analysis; 8081 (50.3%) underwent OE, 1524 (9.5%) HE, and 6448 (40.2%) TMIE. The risk of anastomotic leak was lower after OE (odds ratio [OR], 0.71; 95% CI, 0.62-0.81; $P < .0001$). Overall morbidity rate was 45% (95% CI, 38%-52%) after OE, 40% (95% CI, 25%-59%) after HE, and 37% (95% CI, 32%-43%) after TMIE. Risk estimation showed higher odds of postoperative mortality after OE (OR, 2.22; 95% CI, 1.76-2.81; $P < .0001$) and HE (OR, 1.93; 95% CI, 1.32-2.81; $P < .001$), compared with TMIE. Median length of hospital stay (LOS) was 14.1 (range, 8-28), 12.5 (range, 8-18), and 11.9 (range, 7-30) days after OE, HE and TMIE, respectively ($P = .003$).

Conclusions: HE and TMIE are associated with lower rates of overall morbidity, reduced postoperative mortality, and shorter LOS, compared with OE. TMIE is associated with lower mortality rates and shorter LOS than HE. Further efforts are needed to widely embrace TMIE in a safe manner. (J Thorac Cardiovasc Surg 2022;164:e233-54)

Surgical outcomes; comparison of open, hybrid, and minimally invasive Ivor Lewis approaches.

CENTRAL MESSAGE

Totally minimally invasive esophagectomy is associated with reduced postoperative mortality and shorter length of hospital stay, compared with open and hybrid esophagectomy.

PERSPECTIVE

A comprehensive analysis of reported outcomes after Ivor Lewis esophagectomy was done. Totally minimally invasive esophagectomy was associated with lower rates of overall morbidity, postoperative mortality, and shorter hospital stay, compared with open esophagectomy. Also, totally minimally invasive esophagectomy was associated with lower rates of mortality and shorter hospital stay than hybrid esophagectomy.

See Commentary on page e255.

Video clip is available online.

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Esophageal cancer is one of the most frequent causes of cancer mortality worldwide and has a high rate of disability-adjusted life-years after diagnosis.^{1,2} According to recent cancer statistics, it ranks seventh in terms

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Abbreviations and Acronyms

HE	= hybrid esophagectomy
IRB	= institutional review board
LOS	= length of hospital stay
OE	= open esophagectomy
OR	= odds ratio
TMIE	= totally minimally invasive esophagectomy

of incidence and sixth in overall mortality.³ Although esophageal squamous cell carcinoma is the most prevalent histological type worldwide, a increasing prevalence of esophageal adenocarcinoma has been reported in Western countries.^{4,5}

Esophagectomy is a fundamental mainstay for esophageal cancer treatment.⁶ The Ivor Lewis technique, which was first described in 1946, originally involved a laparotomy and right thoracotomy with an intrathoracic anastomosis.⁷ Since the introduction of endoscopic subtotal esophagectomy using a right thoracoscopic approach in 1992,⁸ minimally invasive surgery has been embraced by several centers in the past 2 decades.⁹⁻¹⁴ However, because a totally minimally invasive transthoracic esophagectomy is a challenging and demanding procedure, some esophageal surgeons still perform open (OE) or hybrid esophagectomy (HE).¹⁵⁻²⁰ The aim of this systematic review and meta-analysis was to compare surgical outcomes between OE, HE, and totally minimally invasive Ivor Lewis esophagectomy (TMIE).

METHODS**Data Sources**

A systematic literature review of articles on OE, HE, and totally minimally invasive esophagectomy (TMIE) was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An electronic search in the Medline database was performed using the following key terms: "Ivor Lewis," "Transthoracic esophagectomy," "Laparoscopy," "Thoracoscopy," "Robotic," "Minimally invasive esophagectomy," "Minimally invasive esophageal surgery," and "Robot-assisted esophagectomy." The institutional review board (IRB) approved this study (IRB approval by Hospital Alemán of Buenos Aires on May 10, 2021. Systematic review and meta-analyses are approved by the IRB of our institution without need for IRB approval number).

Study Selection and Data Extraction

Eligible studies included those that analyzed outcomes for patients who underwent OE, HE, and TMIE. Only patients with an intrathoracic anastomosis were included. OE was defined as laparotomy with thoracotomy. HE was defined as either laparoscopy with thoracotomy or laparotomy with thoracoscopy. TMIE included patients who underwent laparoscopic with thoracoscopic or robot-assisted esophagectomy.

The search strategy was restricted to studies on humans, reported in English, and published between 2000 and 2020. The titles and abstracts identified in the literature search were independently screened by 2 reviewers (C.B.H. and C.A.A.). For studies that included different types of approach

(eg, OE, HE, and TMIE) in the same publication, only those that reported outcomes for each subgroup of patients were included for analysis. In cases in which multiple publications used an overlapping pool of patients, only the larger studies were included.

A total of 4467 articles were initially screened. After removing duplicates and articles that did not meet the inclusion criteria, 4401 articles were reviewed by both authors on the basis of the methodological quality of the publications. Discrepancies between the 2 reviewers were resolved by discussion and consensus with the senior author (F.S.). Finally, 130 articles were included for the meta-analysis. The flow chart on the selection of studies is shown in [Figure E1](#).

The data were carefully evaluated and extracted independently from all of the eligible publications. Information retrieved from the studies included author, publication year, study design, population size, demographic variables, use of neoadjuvant therapy, surgical approach, operative time, anastomotic leak rate, overall morbidity, pneumonia, arrhythmia, mortality, and length of hospital stay (LOS).

Mortality was defined as death before discharge from hospital or within the first 30 postoperative days. From the 130 studies that reported anastomotic leakage rates, 62 defined the diagnosis of anastomotic leak on the basis of at least 1 of the following: radiographic findings, clinical symptoms, endoscopy, methylene blue test, or operative finding.^{21-25,E1-E56,E140} The remaining 68 studies did not report how the anastomotic leak was defined or diagnosed.^{10,E57-E122,E141}

Main Outcomes and Measures

Main outcomes included anastomotic leak rate, overall morbidity, and mortality. Secondary end points included operative time, pneumonia, arrhythmia, and LOS.

Statistical Analysis

The occurrence rate (pooled proportion) and 95% CI were calculated for anastomotic leak rate, overall morbidity, and mortality. Using an a priori assumption of significant heterogeneity, a random effect model was used to estimate pooled proportions and 95% CI. Statistical heterogeneity was assessed using the I^2 statistic, and significance was assumed when the I^2 was greater than 50%. Heterogeneity was also defined as a Cochran Q < 0.10. The summary statistics were treated as independent observations and analyzed using standard methods for independent data. Mean age and mean operative time were compared for patients who underwent OE, HE, and TMIE using the Kruskal-Wallis test. Linear regression was used to model the effect of each approach on the different main outcomes and secondary end points. The parameter for the procedure from the linear model (ie, the log odds ratio in a comparison the 3 approaches) describes differences between groups (TMIE as reference group).

For the main outcomes, publication bias was investigated using funnel plots and the rank correlation test. We used R version 4.1.2 (R Project for Statistical Computing) with meta and metafor packages for all analyses. Statistical tests were 2-sided.

RESULTS

A total of 16,053 patients were included for analysis; 8081 (50.3%) underwent OE, 1524 (9.5%) HE, and 6448 (40.2%) TMIE. Mean operative time was shorter among patients who underwent OE (OE, 286.1 vs HE, 339.3 vs TMIE, 355.6 minutes; $P = .0001$). Patient characteristics are summarized in [Tables E1, E2, and E3](#).

The pooled proportion of anastomotic leak was 6% (95% CI, 5%-7%) after OE, 8% (95% CI, 6%-11%) after

FIGURE 1. Proportion forest plots of anastomotic leak in open, hybrid, and totally minimally invasive Ivor Lewis esophagectomy. *CI*, Confidence interval; *PI*, prediction interval.

FIGURE 1. Continued.

HE, and 8% (95% CI, 6%-9%) after TMIE. It was estimated that the risk of developing an anastomotic leak was significantly lower after OE (odds ratio [OR], 0.71; 95% CI, 0.62-0.81; $P < .0001$), compared with TMIE. A similar risk of anastomotic leak was found among patients who underwent TMIE and HE (OR, 0.90; 95% CI, 0.72-1.13; $P = .37$; Figure 1).

The overall morbidity rate was 45% (95% CI, 38%-52%) after OE, 40% (95% CI, 25%-59%) after HE, and 37% (95% CI, 32%-43%) after TMIE. The risk of overall morbidity was higher after OE (OR, 1.37; 95% CI, 1.26-1.49; $P < .0001$) compared with TMIE. The risk of overall morbidity was similar between TMIE and HE (OR, 1.13; 95% CI, 0.94-1.37; $P = .19$; Figure 2).

The pneumonia rate was 14% (95% CI, 10%-20%), 13% (95% CI, 8%-19%), and 9% (95% CI, 8%-12%) after OE, HE, and TMIE, respectively. The risk of developing pneumonia was higher after OE (OR, 1.14; 95% CI, 1-1.29; $P < .04$), compared with TMIE. Rates of pneumonia were similar for patients who underwent TMIE and HE (OR, 0.85; 95% CI, 0.65-1.11; $P = .24$).

The arrhythmia rate was 8% (95% CI, 6%-12%) after OE, 14% (95% CI, 8%-24%) after HE, and 11% (95% CI, 8%-15%) after TMIE. The risk of developing arrhythmia was lower after OE (OR, 0.53; 95% CI, 0.46-0.63; $P < .0001$), compared with TMIE. The arrhythmia rate was similar among patients who underwent TMIE and HE (OR, 1; 95% CI, 0.77-1.3; $P = .97$).

The pooled mortality rate was 4% (95% CI, 3%-4%) after OE, 4% (95% CI, 3%-6%) after HE, and 2% (95% CI,

2%-3%) after TMIE. Risk estimation showed higher odds of mortality after OE (OR, 2.22; 95% CI, 1.76%-2.81; $P < .0001$) and HE (OR, 1.93; 95% CI, 1.32-2.81; $P < .001$) compared with TMIE (Figure 3).

Median LOS was 14.1 (range, 8-28), 12.5 (range, 8-18), and 11.9 (range, 7-30) days after OE, HE, and TMIE, respectively. Hospital stay was significantly shorter among patients who underwent TMIE ($P = .003$). The main outcomes are summarized in Figure 4. Publication bias was detected for anastomotic leakage and mortality only in OE studies (Figure E2).

DISCUSSION

We aimed to compare postoperative outcomes for OE, HE, and TMIE. Although OE was associated with shorter operative time and reduced anastomotic leakage rates, our study showed that minimally invasive surgery is associated with significantly lower rates of overall morbidity and mortality, along with shorter LOS. In addition, TMIE was associated with lower mortality and shorter LOS than HE.

Ivor Lewis esophagectomy is a complex procedure that is associated with high rates of perioperative complications.^{E10,E85,E123} An open transthoracic esophagectomy has shown overall postoperative adverse events rates as high as 73%, with more than 30% of patients requiring reoperation or intensive care unit admission to treat complications.²¹ Minimally invasive surgery has been adopted by esophageal surgeons to decrease such morbidity rates. Previous studies have shown reduced

FIGURE 1. Continued.

FIGURE 2. Proportion forest plots of overall morbidity in open, hybrid, and totally minimally invasive Ivor Lewis esophagectomy. *CI*, Confidence interval; *PI*, prediction interval.

amounts of intraoperative blood loss, lower rates of pulmonary infection, faster resumption of bowel function, and shorter hospital stay with the use of minimally invasive surgery.^{E37,E124-E127} In line with these findings, our pooled

analysis of a large cohort of patients exposed that patients undergoing OE have higher risks of overall morbidity and mortality, as compared to those undergoing TMIE. The incidence of postoperative pneumonia, specifically, was

FIGURE 2. Continued.

also notably higher after OE. In addition, we also found that open esophagectomies were associated with longer LOS. HE can be considered as an initial step toward performing TMIE.^{E62} Several studies have compared outcomes

for OE and HE.^{19,E62,E72,E89,E128,E129} For instance, a randomized trial showed that HE had considerably lower incidence of intraoperative and major postoperative complications (mainly pulmonary complications) than OE.^{E89}

FIGURE 3. Proportion forest plots of mortality in open, hybrid, and totally minimally invasive Ivor Lewis esophagectomy. *CI*, Confidence interval; *PI*, prediction interval.

Similarly, the MIRO clinical trial compared HE (laparoscopic gastric mobilization with open right thoracotomy) with OE, and also showed higher rates of pulmonary and

major postoperative complications in patients who underwent OE.¹⁹ However, few studies have compared outcomes for HE and TMIE.^{E61,E74,E130} Grimmer and

FIGURE 3. Continued.

colleagues^{E74} compared perioperative results for HE and TMIE, and reported similar LOS and mortality rates between groups. However, pneumonia and wound infections occurred more often in the hybrid group.^{E74} Another study showed that TMIE had a small benefit in terms of blood loss and LOS but similar rates of postoperative complications, compared with HE.^{E130} Interestingly, many studies on surgical outcomes after esophagectomy have included HE in the minimally invasive surgery group (without discrimination between HE and TMIE).^{E131-E134} A critical finding of our study was that patients undergoing HE had considerably higher rates of postoperative mortality and longer LOS than those undergoing TMIE. Therefore, additional efforts are needed to continue embracing a totally minimally invasive approach.

Anastomotic leak is one of the most serious complications after esophagectomy, especially for patients with an intrathoracic anastomosis. Our analysis showed that OE had lower rates of anastomotic leak compared with TMIE and HE. Remarkably, other studies have also shown lower anastomotic leakage rates with the open approach.^{15,E135} For example, Seesing and colleagues¹⁵ performed a propensity score-matched analysis of patients who underwent OE (n = 433) and minimally invasive Ivor Lewis esophagectomy (n = 433), and reported higher leakage rates in the

minimally invasive group (15.5% vs 21.2%; $P = .028$). We hypothesize that these findings are partially explained by the steep learning curve of TMIE.^{E135-E137} For instance, Fumagalli and colleagues^{E138} reported that the mean incidence of anastomotic leakage during the learning curve of TMIE was 18.8%, but it was only 4.5% after the plateau had been reached. In addition, we found that operative time was shorter for OE, and this result could also be influenced by the learning curve of TMIE. In fact, a previous study reported no differences in the operative time between TMIE and OE when performed by experienced surgeons.^{E139}

This study has several limitations. Mainly, most studies included for analysis were retrospective, potentially affected by selection and reporting bias. Furthermore, notable publication bias was detected in OE studies. In addition, important heterogeneity in defining and measuring outcomes was identified among the included studies. Finally, surgical volume (which affects postoperative outcomes after an esophagectomy) was not evaluated. However, the main strength of our study is that we compared outcomes for the 3 different approaches only in patients with intrathoracic anastomosis. The main findings of our study are described in Figure 5 and in a video form related by the first author of the paper (Video 1).

FIGURE 3. Continued.

FIGURE 4. Comparison of surgical outcomes of open, hybrid, and totally minimally invasive Ivor Lewis esophagectomy.

CONCLUSIONS

Although OE was associated with shorter operative time and reduced anastomotic leakage rates, our study showed that HE and TMIE are associated with lower rates of overall morbidity, reduced postoperative mortality, and shorter LOS. In addition, TMIE was

associated with lower mortality rates and shorter LOS than HE. Further efforts are needed to widely embrace TMIE in a safe manner.

Conflict of Interest Statement

The authors reported no conflicts of interest.

Perioperative results after Open vs hybrid vs totally minimally invasive Ivor-Lewis esophagectomy

TMIE was associated with lower rates of overall morbidity, postoperative mortality, and shorter hospital stay, as compared to OE. Also, it was associated with lower mortality and shorter hospital stay than HE. Further efforts are needed to embrace this approach in a safely manner

*OE: Open Ivor lewis esophagectomy, HE: Hybrid Ivor lewis esophagectomy, TMIE: Totally minimally invasive ivor lewis esophagectomy.

FIGURE 5. Main findings of the study. OE, Open esophagectomy; HE, hybrid esophagectomy; TMIE, totally minimally invasive esophagectomy.

VIDEO 1. The first author of the study describes the most relevant findings of the meta-analysis. Video available at: [https://www.jtcvs.org/article/S0022-5223\(22\)00031-9/fulltext](https://www.jtcvs.org/article/S0022-5223(22)00031-9/fulltext).

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: Ivor Lewis esophagectomy, transthoracic esophagectomy, open esophagectomy, hybrid esophagectomy, minimally invasive esophagectomy

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FIGURE E1. Selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses.

FIGURE E2. Funnel plots assessing publication bias for the main outcomes of the study among open, hybrid, and totally minimally invasive esophagectomy.

TABLE E1. Characteristics of studies with patients undergoing open Ivor Lewis esophagectomy

First author reference	Design	Patient N	Median age, years	Male sex, %	Neoadjuvant therapy, %	Mean operative time, minutes	Anastomotic leak, %	Overall morbidity, %	Mortality, %	Median LOS, days
Karl ^{E17}	Retrospective	143	63.7	88.8	19.6	327	3.5	29	2.1	13.5
Griffin ^{E10}	Retrospective	228	64	NA	2.6	257	1.8	52.2	2.2	13
Stilidi ^{E36}	Retrospective	147	57	76.9	0	NA	0	60.6	6.1	NA
Malaisrie ^{E88}	Retrospective	123	62	83.7	25.2	NA	4.1	56.1	2.4	14
D'Journo ^{E69}	Retrospective	102	62	88.2	52.9	NA	1	NA	9.8	28
Jensen ^{E79}	Retrospective	166	62	71.7	8.4	170	1.2	NA	6	11
Junemann-Ramirez ^{E15}	Retrospective	276	66.1	68.1	6.2	NA	5.1	NA	5.8	NA
Homesh ^{E77}	Prospective	41	59	46.3	NA	NA	12	NA	7.3	21.7
Robertson ^{E29}	Retrospective	71	NA	NA	NA	NA	14.1	32.4	8.5	NA
Schröder ^{E98}	Retrospective	126	58.2	84.1	36.5	NA	11.1	54	5.6	NA
Blackmon ^{E63}	Retrospective	214	58	91.1	77	NA	7	NA	NA	12
Akowuah ^{E141}	Retrospective	495	66	NA	NA	NA	6.7	NA	7.5	NA
Chen ^{E68}	Retrospective	196	54	67.3	0	NA	6.6	33.7	2.5	NA
Kono ^{E21}	Retrospective	76	70	92.1	0	500	1.3	NA	1.3	NA
Cerfolio ^{E67}	Retrospective	221	64	62.9	52	234	0.5	49.8	4.5	8
Luechakietisak ^{E22}	Prospective	117	63	83.7	NA	210	5.12	NA	11.1	NA
Raz ^{E28}	Retrospective	33	62	69.7	15.2	NA	0	NA	3	NA
Safranek ^{E30}	Retrospective	40	NA	NA	NA	NA	2.5	NA	0	NA
Wu ^{E47}	Retrospective	73	57	89	0	243	2.7	15.4	2.7	NA
Ott ^{E27}	Retrospective	240	59	94.6	65.4	NA	7.5	NA	2.1	NA
Hamouda ^{E75}	Retrospective	24	60	89.3	83.3	260	8.3	NA	0	14
Pham ^{E97}	Retrospective	46	61	71.7	50	437	10.9	58.7	4.3	14
Munitiz ^{E24}	Retrospective	148	60	87.2	7.4	NA	7.4	34.5	3.4	11
Yu ^{E109}	Retrospective	102	NA	72.5	NA	NA	0	19.6	0	NA
Asteriou ²²	Retrospective	114	61	59.6	0	345	7.9	NA	4.4	11
Kawoosa ^{E81}	Retrospective	177	57	67.2	NA	234	2.8	50.8	3.4	11.2
Vande Walle ^{E102}	Retrospective	54	59	85.2	100	384	9.3	NA	5.6	17.5
Klink ^{E20}	Retrospective	36	62	94.4	72.2	261	11.1	NA	2.8	14
Lee ^{E82}	Retrospective	48	62	100	12.6	270	6.25	35.4	0	15
Noble ^{E26}	Retrospective	53	64	84.9	67.9	240	3.8	60.4	1.9	12
Sayir ^{E32}	Retrospective	60	52.7	43.3	NA	286	5	48.3	5	14
Sihag ^{E99}	Retrospective	76	63.3	80.3	60.5	365	2.6	71	2.6	9
Suttie ^{E39}	Retrospective	140	64	66.4	9.3	NA	7.1	NA	10	21
Beasley ²³	Retrospective	165	66	78.8	41.2	NA	1.2	NA	3	15
Fares ^{E71}	Retrospective	30	56	76.6	NA	269	16.6	NA	16.6	NA
Kauppi ^{E80}	Retrospective	79	63	86	100	367	6.3	60.8	1.3	13
Lindner ^{E85}	Retrospective	134	63	82.8	58.2	275	14.2	53	6.7	21
Ma ^{E87}	Retrospective	167	NA	84.4	NA	208	4.2	20.4	1.8	NA
Mu ^{E93}	Retrospective	90	59	74.4	NA	270	0	8.9	1.1	19
Xie ^{E106}	Retrospective	163	63.8	74.2	0	256	3.7	34.4	2.5	13.9
Zhao ^{E50}	Retrospective	30	57.8	93.3	0	NA	3.3	NA	0	13

(Continued)

TABLE E1. Continued

First author reference	Design	Patient N	Median age, years	Male sex, %	Neoadjuvant therapy, %	Mean operative time, minutes	Anastomotic leak, %	Overall morbidity, %	Mortality, %	Median LOS, days
Harustiak ^{E12}	Retrospective	415	61	86.7	56	NA	13.5	54.7	3.9	12
Li ^{E83}	Prospective	150	60	78.7	NA	202	1.3	30	0.7	16
Peng ^{E96}	Retrospective	31	61.2	80.6	NA	NA	3.2	NA	NA	12.4
Ambrus ^{E57}	Retrospective	25	67.5	76	NA	237	8	NA	4	NA
Bjelovic ^{E62}	Prospective	44	59	81.8	NA	341	0	47.7	2	16.6
Deldycke ^{E7}	Retrospective	322	61.7	80.4	42.5	NA	5.6	NA	NA	NA
Hummel ^{E78}	Retrospective	201	63	81.6	100	205	11	55	3	14
Mei ^{E91}	Retrospective	248	62.4	76.6	0	261	3.2	35	2	12.8
Tapias ^{E41}	Retrospective	75	62.6	89.3	100	361	1.3	NA	2.7	9
Ahmadi ²¹	Retrospective	137	NA	89	59	509	16	73	2	14
Blank ^{E64}	Retrospective	56	NA	85.7	55.4	NA	14.3	57.1	5.4	19
Duan ^{E70}	Retrospective	47	63.6	91.5	0	223	0	12.8	0	15.4
Findlay ^{E72}	Retrospective	187	65	79.3	86.2	NA	5.8	NA	1	11
Miller ^{E23}	Retrospective	45	63	88.9	60	NA	6.7	33.3	0	NA
Zhang ^{E112}	Retrospective	95	63.9	76.8	0	271	5.2	50.5	1.1	12
Fritz ^{E73}	Retrospective	170	64	80.6	65.3	256	24.1	NA	2.9	20
Kesler ^{E18}	Retrospective	278	60	82	71.9	NA	2.9	41.4	1.1	13
Wu ^{E48}	Prospective	75	61	89	NA	NA	2.7	NA	1.5	16
Mariette ^{E89}	Prospective	104	62	83.5	72.1	300	6.7	96	2	14
Wang ^{E103}	Retrospective	325	62	8.2	0	165	5.5	40.3	0.6	12
Wang ^{E45}	Retrospective	87	63	79.3	100	300	2.3	NA	0	10

LOS, Length of stay; NA, not available.

TABLE E2. Characteristics of studies with patients who underwent hybrid Ivor Lewis esophagectomy

First author reference	Design	Patient N	Median age, years	Male sex, %	Neoadjuvant therapy, %	Mean operative time, minutes	Anastomotic leak, %	Overall morbidity, %	Mortality, %	Median LOS, days
Bizekis ^{E61}	Retrospective	35	62	NA	NA	NA	8.6	NA	5.7	9
Godiris-Petit ^{E9}	Prospective	25	60	68	20	260	8	60	8	18
Hölscher ^{E13}	Retrospective	83	61.9	81.9	50.6	NA	6	13.3	NA	NA
Hamouda ^{E75}	Retrospective	25	64	76	80	249	12	NA	0	15
Schröder ^{E33}	Retrospective	419	59.7	83.3	50.1	NA	8.4	NA	4.3	NA
Bludau ^{E65}	Prospective	20	60.9	80	70	NA	5	15	0	NA
Kim ^{E19}	Retrospective	31	64	90.3	0	NA	0	25.8	0	15.2
McCahill ^{E90}	Prospective	11	NA	NA	NA	468	0	81.8	9	13
Bonavina ²⁴	Retrospective	80	63.5	88.8	21.3	300	12.5	NA	2.5	13
Bjelovic ^{E62}	Prospective	44	61.4	84	NA	319	2.3	29.5	2.2	16.1
Wee ^{E104}	Retrospective	20	64	70	85	455	NA	55	0	8
Woodard ^{E46}	Retrospective	131	66	66.4	NA	NA	2.3	NA	0.8	10
Findlay ^{E72}	Retrospective	95	67	88.4	82.1	NA	11.6	NA	4.2	12
Yoshimura ^{E108}	Retrospective	37	69	81.1	2.7	NA	10.8	NA	NA	NA
Asti ^{E58}	Retrospective	100	63	82	42	335	3	29	0	10
Brinkmann ²⁵	Retrospective	154	62	76	80.5	NA	9.7	63	2.6	16
Griminger ^{E74}	Retrospective	25	60.3	84	88	360	4	NA	0	15.8
Hawasli ^{E76}	Retrospective	29	62	89.7	NA	NA	3.4	37.9	6.9	12
Mariette ^{E89}	Prospective	103	59	85.4	74.8	327	10.7	78	1	14
Sdralis ^{E34}	Prospective	57	NA	71.9	64.9	320	14	NA	8.8	12

LOS, Length of stay; NA, not available.

TABLE E3. Characteristics of studies with patients who underwent totally minimally invasive Ivor Lewis esophagectomy

First author reference	Design	Patient N	Median age, years	Male sex, %	Neoadjuvant therapy, %	Mean operative time, minutes	Anastomotic leak, %	Overall morbidity, %	Mortality, %	Median LOS, days
Bizekis ^{E61}	Retrospective	15	62	NA	NA	NA	0	NA	6.6	7
Nguyen ^{E25}	Prospective	51	64	64.7	NA	249	7.8	NA	1.9	9.7
Campos ^{E3}	Retrospective	37	65	86.5	54.1	275	2.7	43.2	NA	10
Hamouda ^{E75}	Retrospective	26	62	96.1	92.3	223	3.8	NA	0	16
Jaroszewski ^{E14}	Retrospective	51	65	84.3	62.7	338	9.8	49	5.9	11
Li ^{E84}	Retrospective	6	55	83.3	0	260	0	0	0	17
Noble ^{E26}	Retrospective	53	66	81.1	75.5	300	9.4	73.6	1.9	12
Luketich ^{E86}	Retrospective	530	64	78.3	28.5	NA	4.3	NA	0.9	7
Sihag ^{E99}	Retrospective	38	61.4	76.3	65.8	360	0	36.8	0	7
Thomay ^{E100}	Retrospective	30	61	86.7	100	535	10	86.7	0	10
de la Fuente ^{E6}	Retrospective	50	66	78	70	445	2	28	0	9
Hernandez ^{E117}	Prospective	52	65	78.8	67.3	442	1.9	26.9	0	NA
Guo ^{E11}	Retrospective	41	60.5	78	NA	268	4.9	12	0	9
Kauppi ^{E80}	Retrospective	74	66	79.2	82.4	359	6.76	50	2.7	13
Mu ^{E93}	Retrospective	52	59	59.6	NA	420	7.7	21.2	1.9	17
Tapias ^{E40}	Retrospective	80	61.5	83.8	68.8	364	0	37.5	0	7
Trugeda ^{E42}	Retrospective	14	56	100	64.3	222	28.6	42.9	0	13
Wu ^{E105}	Retrospective	25	61	64	0	320	4	32	0	13.2
Xie ^{E106}	Retrospective	106	63.2	70.8	0	252	4.7	26.4	1.9	11.8
Zhao ^{E50}	Retrospective	33	57.8	87.9	0	NA	0	NA	0	13
Bongiolatti ^{E66}	Retrospective	8	64	NA	NA	499	25	25	0	10
Campbell ^{E2}	Retrospective	90	62	82.2	66.7	534	13.3	NA	0	12
Mungo ^{E94}	Retrospective	52	66	76.9	65.4	NA	13.5	NA	3.8	9
Cerfolio ^{E4}	Retrospective	85	63	87	75	360	1.3	36.4	3.5	8
Goense ^{E8}	Retrospective	167	65	83.2	91.6	NA	24	NA	NA	NA
Jeon ^{E118}	Retrospective	58	64.3	93.1	NA	371.8	5.2	39.7	1.7	13.6
Mei ^{E91}	Retrospective	131	62.9	76.3	0	252	3	32	2.3	11
Salem ^{E31}	Retrospective	129	67	79.8	76	420	3.8	22.4	1.5	11.5
Straatman ^{E37}	Retrospective	282	62.8	77.3	90.2	333	15.2	43.6	2.1	12
Strosberg ^{E38}	Retrospective	30	64.5	70	70	344	3.3	23.3	3.3	8
Ahmadi ²¹	Retrospective	73	NA	86.3	100	517	14	74	4	10
Brown ^{E1}	Retrospective	49	60.9	81.6	79.6	621	2	NA	6.1	9
Berkelmans ^{E59}	Retrospective	114	66	86	90	NA	21	72.8	0.9	15
Egberts ^{E115}	Retrospective	75	66	68	78.7	392	16	69.3	3	16
Liu ^{E110}	Retrospective	122	61.4	78.7	NA	272	1.6	22.1	NA	NA
Pan ^{E95}	Retrospective	36	64.5	NA	NA	NA	0	25	0	11
Zhang ^{E112}	Retrospective	90	62.9	75.6	0	268	5.6	25.6	1.1	14
Berlth ^{E60}	Retrospective	20	61	95	70	350	15	55	5	13
Dalton ^{E5}	Retrospective	40	63	80	90	374	5	47.5	2.5	9
Grimminger ^{E74}	Retrospective	50	62	82	70	338	14	NA	0	19
Kang ^{E16}	Retrospective	215	62.9	83.3	0	296.7	2.8	27.9	0.5	20
Stenstra ^{E35}	Retrospective	164	64	79.9	NA	270	14.6	40.2	3.7	11
Wu ^{E48}	Prospective	67	62	82	NA	NA	1.5	NA	1.5	15

(Continued)

TABLE E3. Continued

First author reference	Design	Patient N	Median age, years	Male sex, %	Neoadjuvant therapy, %	Mean operative time, minutes	Anastomotic leak, %	Overall morbidity, %	Mortality, %	Median LOS, days
van Workum ^{E43}	Retrospective	561	65	84.1	93.6	268	14.4	61.5	2.3	11
Zhan ^{E49}	Retrospective	257	65.4	74.3	NA	307	6.6	30.4	0.4	13.7
Kukar ^{E51}	Retrospective	121	66	56.2	71.9	463	5	52.9	2.5	8
Meredith ^{E92}	Retrospective	239	64	81.2	77.4	354	3.3	25.9	1.7	9
Pötscher ^{E120}	Retrospective	11	NA	NA	NA	389	18.2	27.3	NA	16.7
Souche ^{E53}	Retrospective	58	62	65.5	87.9	380	31	NA	0	19
Tagkalos ^{E54}	Retrospective	100	63	NA	77	352	15	32	3	31
Valmasoni ^{E101}	Retrospective	10	60.4	90	60	342	10	50	0	NA
Wang ^{E44}	Retrospective	37	62.7	94.6	21.6	340	8.1	45.9	0	10
Wang ^{E140}	Retrospective	216	61	83.8	0	265.5	6.9	50.9	2.3	13
Wang ^{E55}	Retrospective	31	59.7	87	0	387	6.5	19.4	0	12
Wang ^{E121}	Retrospective	24	63	87.5	16.7	352.5	NA	12.5	0	11
Yin ^{E107}	Retrospective	20	64.5	70	NA	267	5	10	0	12.8
Zhang ^{E56}	Retrospective	77	61.6	88.3	20.8	349	6.5	39	0	12.2
Zhang ^{E111}	Retrospective	76	61.8	77.3	0	303.5	11.4	39.3	1.6	9
Awad ^{E113}	Retrospective	100	65.1	80	88	384	6	40	3	10.3
Berlth ^{E114}	Retrospective	100	66	84	84	NA	5	NA	1	11
Gao ^{E116}	Retrospective	34	62	91.2	NA	NA	2.9	29.4	0	10
Merritt ^{E119}	Retrospective	173	62.1	80.3	NA	NA	4	40.5	1.2	8
Shen ^{E52}	Retrospective	102	55	70.6	NA	323.4	5.9	NA	NA	11.5
Zhang ^{E122}	Retrospective	590	61.1	83.9	NA	NA	NA	17.6	1.4	NA

LOS, Length of stay; NA, not available.