

Comparison of Laparoscopic Inversion Esophagectomy and Open Transhiatal Esophagectomy for High-Grade Dysplasia and Stage I Esophageal Adenocarcinoma

Kyle A. Perry, MD; C. Kristian Enestvedt, MD; Thai Pham, MD; Melissa Welker, BS; Blair A. Jobe, MD; John G. Hunter, MD; Brett C. Sheppard, MD

Hypothesis: The perioperative outcomes of laparoscopic inversion esophagectomy (LIE) are comparable to those of open transhiatal esophagectomy (THE), with potential benefits related to the use of minimally invasive techniques.

Design: Case-control study.

Setting: Tertiary care university hospital.

Patients and Interventions: From July 1, 2003, through March 31, 2008, 21 consecutive patients underwent LIE for high-grade dysplasia or clinical stage I esophageal cancer. We compared these patients with 21 stage-matched control patients treated with THE from August 1, 1995, through August 31, 2003.

Main Outcome Measures: Operative time, blood loss, length of hospital stay, perioperative complications, and disease-free survival.

Results: Mean (SD) operative times for LIE (399 [86] minutes) and THE (407 [127] minutes) were not significantly different ($P = .80$). Patients undergoing LIE had significantly lower intraoperative blood loss (168 mL; $P < .001$) and overall length of hospital stay (10 days; $P = .03$) compared with those in the THE group (526 mL and 14 days, respectively). Complication rates were not significantly different between the groups. With a median follow-up of 29 months, there has been 1 systemic recurrence in the LIE group.

Conclusions: Laparoscopic inversion esophagectomy is a safe and effective approach to the treatment of high-grade dysplasia and early esophageal adenocarcinoma. Compared with THE, LIE decreases operative blood loss and length of hospital stay without increasing the operative time, morbidity, or mortality related to esophagectomy.

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THE OPTIMAL TREATMENT FOR patients with high-grade dysplasia (HGD) and early cancer in the setting of Barrett esophagus is controversial. However, despite much interest in radiofrequency ablation, esophagectomy remains the standard treatment for medically fit patients. Transhiatal esophagectomy (THE) has become the preferred approach of many esophageal surgeons in this setting because of decreased morbidity and mortality compared with trans-thoracic approaches. Despite technical advances and improvements in perioperative care, even THE is associated with high morbidity, significant mortality, and lengthy recovery.¹⁻⁴

Interest in minimally invasive esophagectomy has been stimulated by efforts to improve the outcomes and acceptability of THE. Laparoscopic THE was first described by DePaula et al⁵ in 1995, but the widespread acceptance of this approach has

been hampered by impaired visualization of the posterior mediastinum, limited mediastinal work space for lateral esophageal retraction, prolonged operative times, and a difficult learning curve.⁵⁻⁹ Laparoscopic inversion esophagectomy (LIE) simplifies retraction and improves mediastinal visualization during esophageal resection, thus simplifying the operation while maintaining the potential advantages of minimally invasive and 2-cavity approaches.^{10,11}

The aim of this series was to compare operative outcomes for LIE with those of THE in patients with HGD and clinical stage I esophageal adenocarcinoma.

METHODS

PATIENTS

Twenty-one patients underwent LIE for HGD or clinical stage 0 or I esophageal adenocarcinoma from July 1, 2003, through March 31, 2008, at Oregon Health & Science University

Author Affiliations:

Department of Surgery, Oregon Health & Science University, Portland (Drs Perry, Enestvedt, Pham, Hunter, and Sheppard and Ms Welker); and Division of Thoracic and Foregut Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Jobe).

(n=18) and Portland Veterans Affairs Medical Center, Portland, Oregon (n=3). We compared these patients with 21 stage-matched historical control patients who underwent THE at Oregon Health & Science University from August 1, 1995, through August 31, 2002.

Patient data are maintained in a prospective database approved by our institutional review board. Data collected include age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), American Society of Anesthesiologists classification,¹² clinical stage, pathological stage, operative time, intraoperative blood loss, units of blood transfused, intraoperative intravenous fluid volume, method of postoperative analgesia, length of hospital stay, length of intensive care unit stay, complications, and perioperative mortality (defined as all 30-day and in-hospital mortality).

PREOPERATIVE EVALUATION AND PATIENT PREPARATION

Barrett esophagus with accompanying HGD or adenocarcinoma was diagnosed during upper endoscopy with biopsy. Patients found to have esophageal cancer also underwent evaluation with endoscopic ultrasonography and computed tomography of the chest, abdomen, and pelvis.

Patients received preoperative beta-blockade as indicated by the American College of Cardiology/American Heart Association guidelines.¹³ Prophylaxis against deep vein thrombosis was accomplished by the placement of lower extremity sequential devices before anesthesia induction and the addition of subcutaneous heparin therapy postoperatively.

OPERATIVE APPROACHES

Laparoscopic inversion esophagectomy is performed with the patient in the supine, split-legged position as previously described.^{10,11} The operation begins with the hiatal dissection and division of the left gastric artery at its base with a vascular stapler. The short gastric vessels are divided and the posterior stomach is mobilized. A complete Kocher maneuver is performed to allow mobilization of the pylorus to the level of the esophageal hiatus. A 4- to 5-cm-wide stapled gastric tube is created beginning along the lesser curve 6 cm proximal to the pylorus. The distal esophagus is mobilized with its accompanying lymphatic tissue as far proximally as can be safely visualized through the diaphragmatic hiatus, typically from the pericardium to the aorta and pleura to pleura.

At this point, the cervical esophagus is exposed in the left neck, and a transection point is chosen. The proximal stomach is divided with a stapler just below the gastroesophageal junction. Next, a vein stripper is passed distally via a cervical esophagotomy. Within the abdomen, the vein stripper is retrieved through a small gastrotomy made in the staple line and attached to the anvil extracorporeally, allowing for esophageal inversion when the anvil is withdrawn. A U-stitch of sturdy suture around the vein stripper ensures that it will not be dislodged during stripping, and a long suture on the end of the vein stripper maintains the mediastinal tunnel for gastric pull-up as the esophagus is inverted. As the vein stripper is pulled back from the cervical esophagus, esophageal inversion places the mediastinal attachments on tension, enabling their division under direct vision. Inversion provides excellent visualization of the posterior esophageal structures to the level of the inferior pulmonary veins. At the completion of the resection, the proximal stomach and left gastric pedicle are placed in a specimen bag and removed through an enlarged port site. A chest tube is attached to the mediastinal suture in the neck and pulled into the abdomen, where the conduit is sutured to the chest tube.

The neoesophagus is guided through the hiatus with 2 laparoscopic graspers under direct vision as the chest tube is pulled cephalad. Finally, a laparoscopic feeding jejunostomy tube is placed, and the gastroesophageal anastomosis is created using the linear stapled technique described by Orringer et al.⁴ The gastric staple line is oriented posteriorly, and the neoesophagus is elevated to the skin level. A vertical gastrotomy is performed, and an end-to-side stapled esophagogastrotomy is created using a 3.5-mm linear stapler. A nasogastric tube is passed into the conduit, and the resultant gastrotomy is closed in a 2-layer hand-sewn fashion.

Transhiatal esophagectomy is performed via upper midline laparotomy with the patient in the supine position. The left lobe of the liver is mobilized and retracted to expose the esophageal hiatus. A complete gastric mobilization is performed by dividing the short gastric vessels, the left gastric vessels, and the greater omentum. A full Kocher maneuver allows mobilization of the pylorus to the diaphragmatic hiatus. In these patients, a pyloroplasty is performed and a feeding jejunostomy is placed. The cervical esophagus is exposed in the left aspect of the neck and dissected using blunt finger dissection. After division of the phrenic vein and opening of the esophageal hiatus to facilitate visualization, the thoracic esophagus is mobilized under direct vision as far cephalad as can be safely visualized. The dissection is completed using the blunt finger technique. A 4- to 5-cm gastric tube is created using serial firings of a gastrointestinal anastomosis stapler beginning at a point 6 cm proximal to the pylorus. A gastric pull-up reconstruction is performed, and a hand-sewn cervical esophagogastrotomy created. With either technique, the left gastric artery lymph nodes are removed en bloc with the specimen, and the lower mediastinal lymph nodes are removed as a separate specimen.

STATISTICAL ANALYSIS

Data were tested for normality and are presented as mean (SD) or median (interquartile range) where appropriate. Statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina). Analysis of continuous variables was performed using the 2-tailed, unpaired *t* test or the Mann-Whitney test as appropriate, and the χ^2 test was used for dichotomous variables.

RESULTS

Table 1 outlines the patient demographics and operative indications for each patient group. The groups did not differ in terms of sex or American Society of Anesthesiologists classification. The patients undergoing LIE were slightly older (mean age, 69 [8] years) and had lower body mass indexes (mean, 28 [3]) compared with those undergoing THE (61 [9] years [*P*=.003] and 32 [7] [*P*=.03], respectively). Laparoscopic inversion esophagectomy was performed in 10 patients with HGD and 11 with adenocarcinoma. By comparison, 13 patients in the THE group had HGD, whereas 8 had adenocarcinoma. One patient in the LIE group required conversion to laparotomy owing to upper abdominal adhesions from a previous abdominal surgery.

On pathological examination, complete resection of cancer and metaplastic tissue was accomplished in all patients. Disease in 2 patients in the LIE group was upstaged from HGD to stage I adenocarcinoma, and 1 patient with suspected early cancer was found to have HGD. One patient with a suspected intramucosal cancer was

Table 1. Characteristics and Operative Indications for Patients Who Underwent LIE or THE

Characteristic	LIE Group (n=21)	THE Group (n=21)	P Value
Age, mean (SD), y	69 (8)	61 (9)	.003 ^a
Male, No. (%)	18 (86)	17 (81)	.68 ^b
BMI, mean (SD)	28 (3)	32 (7)	.03 ^a
ASA class, No. (%)			
1-2	13 (62)	13 (62)	.59 ^b
3-4	8 (38)	8 (38)	
Operative indication, No. (%)			
HGD	10 (48)	13 (62)	.35 ^b
Clinical stage adenocarcinoma	11 (52)	8 (38)	

Abbreviations: ASA, American Society of Anesthesiologists physical classification system¹²; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HGD, high-grade dysplasia; LIE, laparoscopic inversion esophagectomy; THE, open transhiatal esophagectomy.

^aCalculated using the 2-tailed, unpaired *t* test.

^bCalculated using the χ^2 test.

found to have a T2 lesion with 2 positive lymph nodes. Among patients undergoing THE, 2 patients with suspected HGD were found to have early adenocarcinoma, and clinical stage I tumors in 2 patients were upstaged to stage IIA cancers. The median lymph node yield was 10 (4-12) for LIE and 3 (0-7) for THE (*P* = .005).

The operative outcomes of LIE and THE are given in **Table 2**. Inversion esophagectomy had a mean operative time of 399 (86) minutes compared with 408 (127) minutes for THE (*P* = .80). For LIE, the mean operative time decreased from 453 (83) minutes for the first 10 cases to 351 (56) minutes for the last 11. Mean operative blood loss was lower for LIE (*P* < .001). There was no significant difference in the mean volume of intraoperative fluid (*P* = .64) or the need for blood transfusion (*P* = .87). The LIE patients had a shorter overall median length of hospital stay of 10 (8-14) days, compared with 14 (10-19) days after THE (*P* = .03), but there was no significant difference in length of the intensive care unit stay (*P* = .15). Epidural postoperative analgesia was required in 14 patients in the THE group (67%) but in only 1 patient undergoing LIE (5%).

Major and minor operative complications after LIE and THE are outlined in **Table 3**. The most common complications in this series were atrial arrhythmias and anastomotic leak. There were no perioperative deaths in the LIE group (Table 1). One patient died after THE because of an exacerbation of congestive heart failure.

The overall complication rates did not differ significantly between LIE (13 patients [62%]) and THE (17 [81%]; *P* = .17). Eight patients in the LIE group (38%) developed major complications compared with 12 in the THE group (57%) (*P* = .22), whereas minor complications occurred in 8 (38%) and 7 (33%), respectively (*P* = .75). Atrial arrhythmias occurred in 4 patients in the LIE group (19%) and 7 patients in the THE group (33%) (*P* = .29). Anastomotic leak occurred in 4 patients in the LIE group (19%) and 6 undergoing THE (29%) (*P* = .47). Three patients in each group developed anastomotic strictures that required dilation, but only 1 of these occurred in a patient after a clinically evident anastomotic leak. No adjacent organ injuries oc-

Table 2. Comparison of Operative Outcomes for LIE and THE

Outcome Measure	LIE Group (n=21)	THE Group (n=21)	P Value
Operative time, mean (SD), min	399 (86)	408 (127)	.80 ^a
Operative blood loss, mean (SD), mL	168 (149)	526 (289)	<.001 ^a
Intraoperative fluid volume, mean (SD), mL	5905 (1588)	6169 (2035)	.64 ^a
LOS, median (IQR), d	10 (8-14)	14 (10-19)	.03 ^b
ICU stay, median (IQR), d	2 (2-4)	3 (2-10)	.15 ^b
Perioperative mortality, No. (%)	0	1 (5)	.31 ^c
Type of analgesia, No. (%)			
PCA	20 (95)	7 (33)	<.001 ^c
Epidural	1 (5)	14 (67)	

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LIE, laparoscopic inversion esophagectomy; LOS, length of hospital stay; PCA, patient-controlled intravenous analgesia; THE, open transhiatal esophagectomy.

^aCalculated using the 2-tailed, unpaired *t* test.

^bCalculated using the Mann-Whitney test.

^cCalculated using the χ^2 test.

Table 3. Comparison of Complications After LIE and THE

Complications	Group, No. (%)		P Value ^a
	LIE (n=21)	THE (n=21)	
Major			
Acute myocardial infarction	1 (5)	1 (5)	>.99
Deep vein thrombosis	0	0	>.99
Pulmonary embolus	0	0	>.99
Pneumonia	2 (10)	1 (5)	.55
Adult respiratory distress syndrome	0	2 (10)	.15
Recurrent laryngeal nerve injury	1 (5)	2 (10)	.55
Anastomotic leak	4 (19)	6 (29)	.47
Anastomotic stricture	3 (14)	3 (14)	>.99
Tracheal laceration	0	1 (5)	.55
Splenic laceration	0	1 (5)	.55
Minor			
Atrial arrhythmia	4 (19)	7 (33)	.29
Delayed gastric emptying	2 (10)	1 (5)	.55
Pleural effusion	3 (14)	3 (14)	>.99
Wound infection	2 (10)	3 (14)	.63

Abbreviations: LIE, laparoscopic inversion esophagectomy; THE, open transhiatal esophagectomy.

^aCalculated using the χ^2 test.

curred during LIE. In the THE group, 1 patient incurred a splenic laceration that required a splenectomy for hemorrhage control and another had an injury to the membranous trachea that was repaired via thoracotomy. There were no differences between groups for vocal cord dysfunction, delayed gastric emptying, or wound complications.

At a median follow-up interval of 30 months, 3 patients developed recurrent esophageal cancer, 1 after LIE and 2 after THE. There were no local recurrences, and each of these patients presented with a systemic recurrence 29 to 48 months after resection of a stage I esophageal adenocarcinoma.

The aim of this study was to compare the perioperative outcomes after LIE and open THE for HGD and early esophageal adenocarcinoma. We found that LIE can be performed in the same amount of time as open THE, with significantly decreased operative blood loss and overall length of hospital stay. There were no significant differences in complication rates or disease recurrence between these approaches in this series.

Some authors have suggested that minimally invasive approaches to esophagectomy have failed to gain wide acceptance because of, in part, prolonged operative times.¹⁴ In this series, we demonstrated that operative times for LIE were equivalent to those required for THE. Furthermore, experience with the LIE technique led to decreased operative times (from 453 minutes for the first 10 cases to 351 minutes for the last 11 cases). Although some might consider the operative times to be long for LIE and THE, the participation of trainees in these operations extends the times in most cases. As experience with this technique is gained, further reductions in operative times are anticipated.

Multiple authors have demonstrated survival benefits of decreased operative blood loss and transfusion requirements for many oncologic resections, including esophagectomy.¹⁵⁻²¹ In this study, LIE resulted in a significantly lower intraoperative blood loss than did THE. Three patients in each group required a blood transfusion; however, in the LIE arm these patients each received a single unit of blood, whereas those in the THE group received multiple units of packed red blood cells. Larger studies are required to quantify differences in the rate of blood transfusion during open and laparoscopic esophagectomy and its effect on outcomes. The favorable operative characteristics, including decreased operative blood loss afforded by the laparoscopic approach, may especially benefit elderly or medically frail patients who are more sensitive to operative stress.

Many studies have shown that minimally invasive surgery decreases the length of hospital stay and leads to faster recovery and return to normal function compared with open surgery.²²⁻²⁹ In this study, LIE was associated with a significantly shorter length of hospital stay compared with THE, although the duration of the intensive care unit stay was not significantly different. One possible explanation for the shorter length of stay after minimally invasive esophagectomy is the method and adequacy of postoperative analgesia. In this series, adequate pain relief was achieved using intravenous patient-controlled analgesia in 20 of the 21 patients undergoing LIE. Two-thirds of patients in the THE group required epidural analgesia for postoperative pain control. The use of historical controls in this study may also affect the length of stay findings owing to the increased emphasis on length of hospital stay as a quality of care indicator in recent years. Prospective studies using validated pain scores are required to prove decreased postoperative pain, increased early patient mobilization, and a faster return to normal function after LIE.

Another proposed benefit of minimally invasive esophagectomy is decreased cardiopulmonary morbidity compared with open approaches. Although not statistically significant, atrial arrhythmias occurred in 33% of patients undergoing THE and 19% of patients after LIE. Decreased pulmonary morbidity is an acknowledged benefit of THE compared with transthoracic approaches. Although LIE did not result in a decreased incidence of pneumonia or pleural effusion compared with THE, LIE does not appear to be associated with an increased risk of respiratory complications.

Anastomotic leak remains a significant risk of esophagectomy with gastric pull-up reconstruction, regardless of the approach chosen. In our series, LIE was associated with a 19% anastomotic leak rate compared with 29% after open THE. Although not a significant difference, the lower leak rates with LIE could be explained in several ways. First, the anastomoses in the LIE group were created using the stapled technique described by Orringer et al,⁴ whereas the THE anastomoses were hand sewn. In previous studies, the stapled cervical esophagogastrotomy has been shown to produce lower anastomotic leak rates than hand-sewn approaches.⁴ Another potential contributor is transient gastric ischemia after creation of the gastric conduit, and further studies are required to quantify its role in the development of postoperative anastomotic leaks and strictures.

The limitations of this study include the nonrandomized, noncontemporaneous nature of the cohorts and the relatively small sample size. Most of the patients with esophageal cancer treated at our center during the study period underwent open or minimally invasive Ivor-Lewis or 3-field esophagectomy for locally advanced cancers and were not included in this study. The low number of lymph nodes sampled, particularly in the THE group, may also be considered by some as a weakness of this study.

In conclusion, LIE is well suited for the treatment of HGD and early cancers of the distal esophagus and gastroesophageal junction. This technique can be performed safely in the same amount of time as that for conventional open THE, with less intraoperative blood loss and shorter duration of hospital stay. Future prospective studies with larger cohorts may demonstrate improvements in postoperative cardiac, pulmonary, and infectious complications.

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Correspondence: Brett C. Sheppard, MD, Department of Surgery, Oregon Health & Science University, Mail Code L223A, 3181 Sam Jackson Park Rd, Portland, OR 97239.

Author Contributions: Dr Sheppard had full access to all of the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis. *Study concept and design:* Perry, Enestvedt, Jobe, Hunter, and Sheppard. *Acquisition of data:* Perry, Welker, Jobe, Hunter, and Sheppard. *Analysis and interpretation of data:* Perry, Enestvedt, Pham, Hunter, and Sheppard. *Drafting of the manuscript:* Perry, Enestvedt, Pham, and Welker. *Critical revision of the manuscript for important intellectual content:* Perry, Enestvedt, Pham, Jobe, Hunter, and Sheppard. *Study supervision:* Jobe, Hunter, and Sheppard.

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DISCUSSION

Vic Velanovich, MD, Detroit, Michigan: The adoption of new techniques rests on meeting 1 or more key criteria: The technique allows us (1) to do something that we haven't been able to do before; (2) to do something we have already been doing, but do it better; (3) to make the treatment easier on the patient, with equivalent results; and (4) to be cheaper, with equivalent results. Therefore, we need to use the results of this study as evidence of LIE meeting these criteria.

Clearly, LIE does not allow us to do something we couldn't do before. Does it let us do esophagectomy better? The complication rates were nearly equivalent. There was less blood loss, but, even though it was statistically significant, was it clinically significant?

There was no difference in transfusion rates, so it's hard to say. There appeared to be about a 20% difference in overall complication rate, but this was not statistically significant. Was this a β error?

Does this technique make things easier on the patient? As with other minimally invasive techniques, we like to think so. My bias is to believe so, but we have no data. Do you have any information on postoperative symptoms, quality of life, return to daily activity, or patient satisfaction? I am reminded of a quote attributed to Sir Alfred Cushieri that, when the access trauma exceeds the operative trauma, then a minimally invasive approach makes sense; when the operative trauma exceeds the access trauma, it doesn't. The issue is which is the greater trauma in esophagectomy.

Is it cheaper? Again, no data. The authors do report a shorter length of stay, but, given that the operations were done during 2 different time periods, it is hard to interpret this. Do you have any information on the cost of the operation and postoperative care compared to THE?

Two final questions: Do you follow your patients with upper endoscopy postoperatively? If you do, what is the Barrett's recurrence rate? Lastly, LIE is not the most minimally invasive approach to Barrett esophagus with or without HGD. What are your thoughts comparing LIE to endoscopic radiofrequency or cryoablation?

Dr Sheppard: Regarding the question about type II or β error, this is indeed a small series. When we started, we felt that we would need to show about a 40% difference, given the limited numbers, to make any statement on significance. Clearly, this is a limitation of the study. It just gives us some suggestion of where we are.

Are our patients better off? Currently we do not have quality-of-life data for the association, and we absolutely need to do that as we have done for other series out of our institution. However, in the office our patients seem to benefit from the reduced trauma of the laparoscopic approach. We feel the procedure has less trauma, it is done under direct observation, and there is sharper dissection and less blunt dissection. Is this beneficial? Given the limitations of the study, we have some hints. There are about 10% less atrial arrhythmia. We attribute this to a more meticulous and less traumatic dissection below the pericardium. There is less blood loss and, while this did not achieve statistical difference, those patients in the laparoscopic group who needed blood received about 1 U of blood, while those patients in the open group received about 3 U of blood. We would like to get this down to zero but, given the work that you and others are doing with the Michigan American College of Surgeons National Surgical Quality Improve-

ment Program collaborative regarding the impact of blood transfusion, we think this is an improvement.

Finally, about 95% of our patients could be managed with patient-controlled analgesia and oral pain medication and did not require epidural anesthesia. This is in direct contrast to the open group, where the majority of them did have epidural anesthesia and, as was mentioned earlier, there was a longer length of stay.

Regarding cost, it is a difficult thing to analyze. We have not looked at this. The operative times between laparoscopic and open surgeries are about the same. The instrument costs are probably a bit higher for laparoscopic. Pain control is probably a bit less expensive, and length of stay is a bit less expensive. If we looked at it, it probably would be a wash, but I don't really have the evidence.

We do not follow our patients with upper endoscopy, so I don't have an answer for you regarding Barrett's recurrence. In terms of other minimally invasive techniques, they are promising. I would like to watch them mature before I compare them to LIE.

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In these days of cost containment, we would like authors to submit articles on the costs of items in the operating room. Specifically, we are interested in cost comparisons between manufacturers on items such as implants, meshes, or specific sutures or dressings. By providing our readership with cost comparisons, we may be able to do better when making choices in the operating room. We request that articles have tables with cost comparisons.