As submitted to:

Journal of the American College of Surgeons

And later published as:

Oncologic efficacy is not compromised, and may be improved with minimally invasive esophagectomy

Volume 212, Issue 4, April 2011, Pages 560-566

10.1016/j.jamcollsurg.2010.12.042

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Presented at the 122nd Annual Meeting of the Southern Surgical Association, Palm Beach, FL; December 2010.

Running Title: Minimally Invasive Esophagectomy

Key Words; esophagectomy, esophageal cancer, lymph nodes, complications

ABSTRACT

Introduction: Esophageal cancer rates are increasing rapidly. Major morbidity and mortality rates continue to be quite high in large series of trans-thoracic esophagectomies. Minimally invasive approaches to esophagectomy are increasingly being utilized. We compare our growing series of minimally-invasive (combined thoracoscopic and laparoscopic) esophagectomies (MIE) to a contemporary series of open, trans-thoracic esophagectomy.

Methods: We queried a prospectively maintained IRB-approved esophagectomy database at Thomas Jefferson University Hospital to identify 65 patients who underwent a MIE with only a thoracoscopic component (n=11), or minimally-invasive Ivor Lewis approach (n=2), or minimally-invasive three-hole approach (true MIE, n=52). The majority of these were performed in the last 18 months. These patients were compared to a group of 53 patients who underwent open Ivor-Lewis esophagectomy (n=15) or open three-hole esophagectomy (n=38) over the last 10 years. Perioperative complications were graded using a variation of the Clavien scale.

Results: The MIE and open groups were similar in terms of gender (75% male in both groups) and average age (61 vs. 62 years, respectively). The majority of patients in the open group underwent neoadjuvant chemoradiation therapy (81%) due to institutional preferences at the time; a significantly smaller (43%) number of patients in the MIE group underwent neoadjuvant therapy ($p<0.0001$). In terms of oncologic efficacy, 97% and 94% of patients in both groups underwent R0 resections. Patients undergoing MIE had a significant increase in the number of harvested LN (median=20 vs. 9 nodes, $p<0.0001$). Pathologic stage was similar between both groups. Length of stay was significantly decreased in patients who underwent MIE (8.5 days vs. 16 days, $p=0.002$). Finally, there were significantly fewer serious complications (grades 3-5) in the MIE group (19% vs. 48%, $p=0.0008$).

Conclusions: In this initial report of a growing single-institution series of MIE, we demonstrate that oncologic efficacy, in terms of completeness of resection and number of harvest LN is not compromised with this approach, and may actually be improved with a significantly increased number of harvested LNs. We also demonstrate this approach is associated with fewer serious complications and significant decrease in the length of postoperative hospital stay.

INTRODUCTION

Esophageal cancer is the eighth most common cause of cancer worldwide [3]. In 2010, it is estimated that there will be 16,640 new cases diagnosed in the U.S. and 14,500 deaths [1]. It often presents at an advanced stage and therefore tends to be incurable. For resectable disease, surgery is the gold standard for treatment. For these patients, who often have considerable co-morbid conditions (obesity, smoking, and diabetes), esophagectomy carries a significant risk of perioperative morbidity and mortality. Mortality rates range from 5-20% [2,3]and morbidity generally occurs in approximately 50% of patients [3]. Many series also report higher rates of complications with trans-thoracic esophagectomy compared to transhiatal esophagectomy [4].

The minimally invasive approach to esophagectomy was first reported by Cuschieri *et al* in 1992 [5]. Since that time, numerous reports have shown that the procedure is safe, feasible, and leads to a favorable outcome for a number of early operative variables when compared to open esophagectomy [6,7, 8]. Additional small series have demonstrated that lymph node retrieval is adequate with MIE [9]and in most cases comparable to that seen with open procedures [10].

The minimally invasive approach to esosphagectomy encompasses three main approaches: (1) laparoscopic transhiatal esophagectomy with anastomosis in the neck, (2) laparoscopic and thoracoscopic Ivor-Lewis esophagectomy, and finally (3) laparoscopic and thoracoscopic three-hole esophagectomy with the anastomosis in the neck (true MIE). There are various other combinations, and early in our experience, we performed the abdominal portion open but the thoracic portions were performed with Video Assisted Thoracoscopic Surgery (VATS). Because many series have demonstrated the morbidity of the open trans-thoracic component, we believe that performing the thoracic portion with VATS provides a substantial benefit. At Thomas Jefferson University Hospital, we have been attempting MIE in all patients since July 2008. We have performed all three of the above-mentioned methods, but the majority are true MIE. This report is our initial analysis of our experience with thoracoscopic and laparoscopic MIE with particular focus on the oncologic efficacy as demonstrated by lymph node retrieval and completeness of resection.

METHODS

Patient Population

We queried our IRB-approved prospective esophagectomy database for patients undergoing esophagectomy for cancer or high-grade dysplasia between 2000 and October 2010. Data collected included type of esophagectomy, age, gender, race, neoadjuvant chemoradiation, history of smoking, completeness of resection, histologic diagnosis, pathologic stage, total number of harvested lymph nodes, length of stay, and perioperative complications. Complications were graded on a scale of 1-5 using a modification of the previous published scale of Clavien *et al* [11]. Any patient with a VATS component that was completed thoracoscopically was included in the analysis because of the known benefits of avoiding a thoracotomy. Patients undergoing surgery with biopsies revealing high-grade dysplasia were also included in this analysis because these patients were treated as if they had cancer because of the high incidence of invasive cancer seen in those who undergo definitive surgery. The breakdown of cases included in the minimally invasive groups is as follows: VATS/laparotomy/neck incision—eleven cases; VATS/Laparoscopy/Ivor-Lewis—two cases; and VATS/laparoscopy/neck incision—52 cases for a total of 65 cases minimally invasive cases.

The database was then queried in an attempt to find a contemporary (after 2000) cohort of patients who underwent esophagectomy with a thoracotomy component. We identified a total of 53 open cases that met these criteria. Similar data were collected in these patients—Ivor-Lewis (n=15) and 3-Hole (n=38). Continuous variables (such as age, length of stay, and total number of lymph nodes (LN) harvested) were compared using Student's t-test. Categorical variables (such as complication grade) were compared using Chi-square. Statistical significance was accepted at $p<0.05$.

Surgical Technique for '3-hole' MIE

Thoracoscopic Portion

The patient is placed in the right lateral decubitus position. The following ports are typically placed: 1) at the anterior axillary line in the 8^{th} intercostal space (10 mm port); 2) at the posterior axillary line in the 7^{th} intercostal space (10 mm); 3) below the tip of the scapula (5 mm); 4) 4th intercostal space in the anterior axillary line (10 mm); and 5) between the 1st and the 4th ports for suction (5 mm). An Endo Stitch is placed at the tendinous portion of the right diaphragm. This is brought through the skin using a Carter-Thompson device and maintained on tension to retract the diaphragm. The dissection starts anteriorly at the pericardium. The harmonic scalpel is used to incise the pleura and separate the periesophageal fat from the pericardium. The subcarinal lymph node package is then completely removed, separating it carefully from the left and right main stem bronchi. The azygous vein is divided with an Endo GIA using a vascular load. Nodal tissue around the esophagus is dissected and brought with the specimen. The esophagus is then carefully separated from the trachea and the dissection then proceeds cephalad to the thoracic inlet. The pleura, posteriorly, is then incised anterior to the thoracic duct. The esophagus and periesophageal tissue are dissected away from the aorta; aortoesophageal branches are clipped and divided. An intercostal block with Marcaine is performed at the level of ribs 6, 7, 8, and 9, and a single chest tube is inserted.

Laparoscopy

The patient is then repositioned in the relaxed lithotomy position. A transumbilical approach is used for insertion of the 12 mm camera port. The remaining 5-mm ports are placed in the right lateral subcostal position and the left subcostal position. A mid-axillary 12-mm port is inserted in the right subcostal position. Using these ports, the greater curvature of the stomach is mobilized, with fastidious preservation of the gastroepiploic arcade. The short gastric vessels are divided and the fundus is mobilized. The greater omentum is divided along the gastroepiploic arcade and the stomach is completely mobilized down to the origin of the right gastroepiploic arterial system. The lesser curve is then mobilized and the right diaphragmatic crus identified. The phrenoesophageal ligament is incised and the retrocardia space is established. The right crus is opened by incising it with the Harmonic scalpel to allow for easy placement of the conduit. At this point, the left gastric artery is divided with the endovascular GIA stapler, and the nodal tissue is swept up with the specimen. Next, the 12 mm port site is enlarged to an approximately 5 cm incision and a Lap Disk wound protector is inserted.

Neck incision and completion

The left neck is approached through an oblique incision paralleling the anterior border of the sternocleidomastoid. The platysma and strap muscles are divided as is the inferior thyroid artery. The left recurrent largyngeal nerve is identified and preserved throughout its course. The esophagus is then encircled and transected with a GIA-75 linear cutting stapler. The distal end of the divided esophagus is attached to a chest tube as a mediastinal placeholder and delivered with the stomach through the wound protector in the right upper quadrant small incision. The stomach is tubularized extracorporeally with a GIA-75 stapler and the suture line is oversewn with a running 3-0 PDS suture. A pyloromyotomy is also performed through this incision. The proximal tip of the stomach tube is then attached to the mediastinal chest tube placeholder and the stomach, in proper orientation, is delivered back up into the left neck, where a side-to-side esophagogastrostomy anastomosis is performed with an Endo GIA stapler. The nasogastric tube is positioned through this anastomosis. The anastomosis is then completed with a TA-60 stapler. A tacking suture is then placed from the staple line to the prevertebral fascia to keep this anastomosis in the neck region. At this point, a #14 French red rubber catheter is placed laparoscopically as a feeding jejunostomy tube.

Synopsis of surgical technique for Ivor-Lewis MIE

The operation is begun with the patient in relaxed lithotomy position and the laparoscopic portion is performed as above. At the completion, the conduit is placed back into the abdominal cavity in the correct orientation so that it can be delivered into the chest for the next portion. The patient is then placed in the right lateral decubitus position and VATS ports are placed as above. The dissection proceeds as previously described except for that done towards the thoracic inlet. Once the esophagus is dissected circumferentially to the level of the azygous vein, it is sharply divided at this level and removed through a slightly enlarged posterior surgeon's port (#2, above).

At this point, a 29 EEA anvil is placed inside the esophagus. An EndoStitch is used to create a pursestring to secure the anvil in the esophageal lumen. The conduit is grasped and opened so that the EEA shaft can be placed into it. The spike from the EEA is brought out from the side of the conduit and docked into the anvil. The EEA is then fired and removed. At this point, an Endo GIA blue load is used to amputate that tip of the stomach and remove it from the chest. Another EndoStitch is used to tack the stomach to the diaphragmatic crura. The intercostal nerve block and chest tube placement proceed as described above.

RESULTS

Demographics (Table 1)

The groups were relatively equally matched in terms of demographic data (Table 1). The average age in the open group was slightly higher at 62 years although this was not a significant difference (p=0.6). The majority of patients in both groups were male. Finally, the vast majority of patients in the minimally invasive group (94%) had adenocarcinoma (n=55) or high-grade dysplasia (n=5), which reflects recent trends at TJUH where it is rare to see a patient with squamous cell carcinoma of the esophagus and even rarer for them to undergo esophagectomy. There were significantly more patients in open group who underwent neoadjuvant chemoradiation (81% vs. 43%). Finally, the patients were well distributed by pathologic stage—about 30% of patients in both groups had a stage 0 tumor. The majority of these were patients who had pathologic complete response to neoadjuvant chemoradiation.

Type of Surgery

In the minimally invasive group (n=65), there were eleven patients who underwent VATS with laparotomy and an anastomosis in the neck. Some of these patients were early in our experience (most in 2004 and 2005). There were also five patients who were intended to have MIE but the abdominal portion was unable to be completed laparoscopically due to severe adhesions from previous abdominal surgery. The majority of patients in the MIE group (n=52) underwent both a thoracoscopic and a laparoscopic component with the esophagogastric anastomosis being performed in the neck. Two patients had the thoracoscopic/laparoscopic components with Ivor-Lewis type anastomosis.

In the open group, we chose for comparison a group of patients who underwent a thoracotomy as part of their esophagectomy. These patients stretched back to 2000, because the majority of recent cases are being done without a thoracotomy. In total, there were 15 patients who underwent Ivor-Lewis esophagectomy with an anastomosis in the chest and 38 patients who underwent 3-hole esophagectomy with an anastomosis in the neck. In the same time period, there were no other trans-thoracic esophagectomies and there were 76 open, transhiatal esophagectomies. Figure 1 demonstrates the overall volume and surgical trends at TJUH from 2000 to 2010. There were no major differences in perioperative variables for patients in either of the open groups in terms of blood loss, length of stay and nodal yields.

Perioperative Complications (Table 2)

There were five perioperative deaths (8%) in the MIE and four (8%) in the open group. This difference was not statistically significant. Of the five deaths in the MIE cohort, one was a sudden, unexplained, death on post-operative day one; the other four patients developed pneumonia and respiratory failure, which led to their demise. Of these five deaths in the MIE cohort, there were three deaths in the laparoscopy/thoracoscopy group (6%) and two deaths in the thoracoscopy/laparotomy group (18%). In the open group, the four patients who died suffered from gastric conduit necrosis, ischemic bowel, ARDS, and pneumonia/respiratory failure (one each). In terms of overall complications (Table 2), the rate was slightly higher in the open group (60% vs. 48%, p=0.1). We did find a significantly higher rate of major complications (grades 3 and above) in the open group (41% vs. 20%). As expected, there was a higher rate of pneumonia in the open group (18%), and only 7.7% in the MIE group, but this difference was not statistically significant. There were two major complication rates which were significantly higher in the open group. The rate of respiratory failure and ARDS in the open group (21%) was significantly higher than that observed in the MIE cohort (7.7%, p=0.03). Additionally the 11% rate of DVT/PE in the open group was significantly increased compared to the 1.5% seen in the MIE group (p=0.04). The rate of anastomotic leaks was equal in both groups. The most common minor complications were wound infections and supraventricular arrhythmia; there were no significant differences between groups for these minor complications.

Surgical Outcomes (Table 3)

The average blood loss was significantly lower for patients who underwent MIE as compared to those who had open surgery (182 vs. 619ml, p<0.0001). Additionally, the median length of stay (9 vs. 16 days) was significantly less in patients who underwent the minimally invasive approach (p=0.003). The R0 resection rates were high in both groups, and there were no differences between the groups. All five of the R1 resections consisted of the circumferential margins being positive and not margins on the esophagus or stomach themselves. Finally, we did note a significant increase in nodal harvest in the MIE group (median-20 vs. 9, p<0.0001).

DISCUSSION

Since its first description in 1992, minimally invasive esophagectomy (MIE) has become more and more prevalent with numerous reports of large series appearing in the literature. In a recent review from England, Lazzarino *et al* demonstrate that the percentage of minimally invasive esophagectomies being performed there has increased from 0.6% in 1996/1997 to 16% in 2007/2008 [6]. With the increasing frequency of this operation, it is incumbent on investigators to ensure that not only is this operation safe but that the oncologic outcomes are equivalent to that of the open operation.

When laparoscopic colectomy for cancer was first introduced, there was a concern about port-site recurrences and oncologic efficacy [12,13]. However, several randomized prospective trials demonstrated that the laparoscopic approach was not only safe, but oncologically sound. The COST trial (n=872) demonstrated equivalent nodal yields, recurrence-free, and overall survival with shorter hospital stay and decreased narcotic use in patients with colon cancer [14]. The COLOR trial from Europe (n=1248) also demonstrated equivalent nodal yields and margin positive resections [15]. Finally, in an analysis of NSQIP data, Bilimoria *et al* demonstrated that laparoscopic colectomy was associated with a significantly decreased rate of any complication and length of stay [16]. In retrospect, early concerns about port-site recurrences and oncologic efficacy now appear unfounded.

There have been many small institutional series that have compared MIE with open, trans-thoracic approaches. In a group of 90 patients undergoing MIE or Ivor-Lewis esophagectomy, Pham *et al* showed that MIE was associated with decreased blood loss and rates of wound infection, but no change in length of stay and cardiovascular and pulmonary complications [7]. They also demonstrated a significant increase in nodal yield with MIE (13 vs. 8). Parameswaran *et al* also compared MIE and Ivor-Lewis esophagectomy in a series of 80 patients. They demonstrated an increased rate of pulmonary complications in the open group (23% vs. 8%). Interestingly, they also demonstrated that nodal yields were significantly higher in the MIE cohort (23 vs. 10) [17]. Finally, in a recent meta-analysis, Nagpal *et al* reviewed 12 studies of 672 patients undergoing MIE and 612 open esophagectomies. This analysis demonstrated that MIE had lower blood loss, shorter hospital stay, and reduced total morbidity and respiratory complications [8].

The current series is one of the largest reported in which MIE is compared to open esophagectomy in a single-institution series. We acknowledge that there are several limitations of our series. First of all, because our current practice is to attempt MIE in virtually every patient, we cannot use a concurrent series of patients for comparison, and instead had to use historical data and attempt to match patients as best as possible. Additionally, this is not a randomized, prospective trial comparing the open technique to MIE. We compared patients undergoing esophagectomy with a thoracoscopic component (eleven with VATS/laparotomy, 52 true MIE, and two MIE/Ivor-Lewis) to those undergoing esophagectomy with an open thoracotomy (15 Ivor-Lewis and 38 three-hole esophagectomies). We confirm many of the findings of the previous series and meta-analyses. Specifically, we demonstrate a significant decrease in major complications for patients undergoing MIE compared to open, trans-thoracic approaches, including decreased incidence of pneumonia, respiratory failure and ARDS. We also demonstrate that blood loss and length of stay are significantly decreased with the minimally invasive approach. Most importantly, we show that R0 resection rates are equal and that lymph node yield is significantly higher as compared to open approaches.

The importance of lymph node yield in numerous cancers is increasingly being demonstrated in numerous gastrointestinal cancers including esophageal cancer [18,19]. It is interesting to speculate why lymph node yields are increased in minimally invasive approaches in not only our series but two others as well [7,17]. It is likely that this is multi-factorial and has to do not only with improved processing on the part of pathology departments, with increased awareness of importance of nodal yields, but also improvements in operative technique. Pham *et al* state that their technique has evolved to include more complete clearance of the celiac node basin [7]. In our thoracoscopic approach, we specifically clear the level 7, 8, and 9 mediastinal nodes. Also, the laparoscopic approach affords a better dissection of the celiac nodes and removal of left gastric nodes by allowing better visualization and the ability to divide the left gastric artery at its origin with the vascular stapler.

It remains to be seen whether this increased nodal yield will result in a survival benefit because the majority of our patients who underwent MIE were operated on in the last 18 months. In one of the earlier randomized trials of laparoscopic colectomy, Lacy *et al*, demonstrated that cancer-specific survival was significantly higher in the laparoscopic group (91% vs. 79%). This benefit was limited almost exclusively to patients with stage III disease [20]. This benefit was not redemonstrated in other larger randomized series. Additionally, in Lazzarino's analysis of MIE in the United Kingdom, there was a suggestion that patients undergoing MIE had better 1-year survival rates than patients undergoing open esophagectomy [6].

Therefore, in conclusion, we demonstrate that minimally invasive approaches to esophagectomy offer several advantages over open ones. These include decreases in the number of major complications, respiratory complications, blood loss and length of stay. At the same time, oncologic efficacy is maintained with equivalent R0 resection rates, and significantly increased nodal yields. It is our feeling that the minimally invasive approach is justified for patients with esophageal cancer, and is safe even in patients who have received neoadjuvant therapy. Future study will need to determine the impact of these approaches on survival.

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TABLES

Table 1—Patient Demographics and Pathology

	Minimally Invasive (n=65)	Open (n=53)	p-value
Age	41-78 (mean=61)	40-86 (mean=62)	0.6
Gender (#male)	51 (78%)	38 (72%)	0.5
Caucasian	55 (85%)	51 (96%)	0.06
Neoadjuvant therapy	28 (43%)	43 (81%)	<0.0001
Adenocarcinoma	55 (85%)	39 (74%)	0.2
Squamous cell carcinoma	4 (6%)	14 (26%)	0.004
High-grade dysplasia	5* (8%)	0	0.06
Pathologic Stage			
0	18 (28%)	17 (32%)	0.7
I	24 (37%)	12 (23%)	0.1
II	10 (15%)	12 (23%)	0.3
III	13 (20%)	10 (19%)	1.0
IV	0	2 (4%)	0.2

* one patient underwent MIE for esophageal melanoma.

TABLE 2

	Minimally Invasive (n=65)	Open (n=53)	p-value
Mortality	5 (7.7%)	4 (7.5%)	1.0
Overall Complications	31 (48%)	32 (60%)	0.1
Major Complications (Grades 3-5)	13 (20%)	23 (41%)	0.008
Minor Complications (Grades 1-2)	18 (28%)	12 (23%)	0.5
Respiratory Failure/ ARDS	5 (7.7%)	12 (21%)	0.03
Pneumonia	5 (7.7%)	10 (18%)	0.11
Anastomotic Leak	9 (14%)	6 (11%)	1.0
DVT/PE	1 (1.5%)	6 (11%)	0.04

DVT—deep venous thrombosis

PE—pulmonary embolism

ARDS—adult respiratory distress syndrome

TABLE 3

	Minimally Invasive (n=65)	Open (n=53)	p-value
Mean EBL (ml)	182	619	<0.0001
Median LOS (days)	9	16	0.003
R0 Resection	63 (97%)	50 (94%)	0.6
Median # harvested LN	20	9	<0.0001

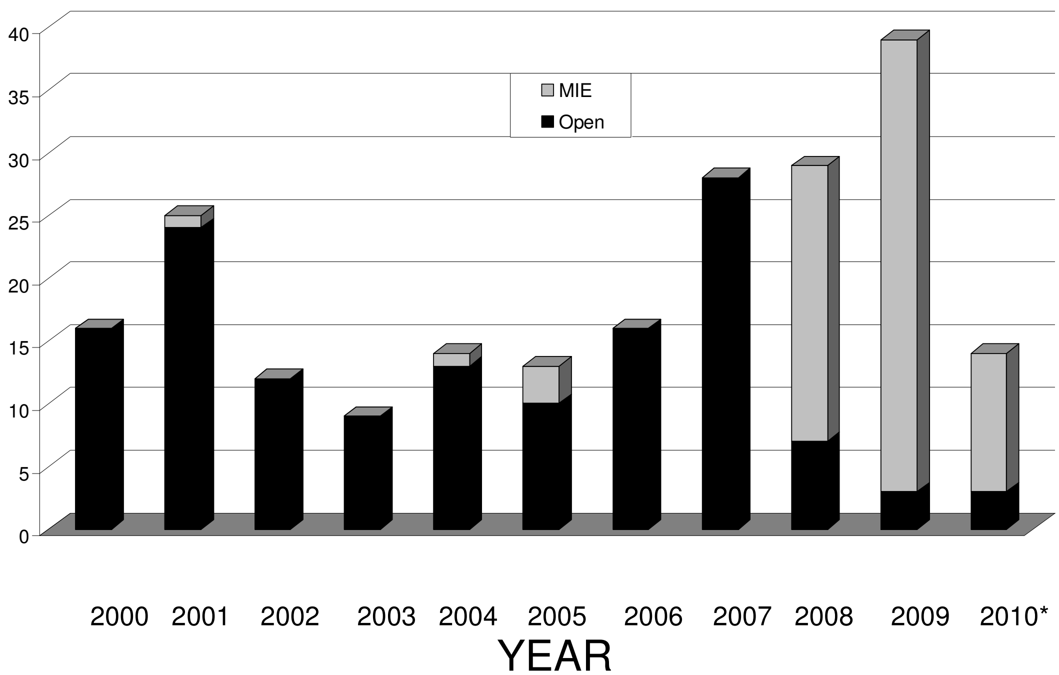
EBL-estimated blood loss

LOS—length of stay

LN—lymph nodes

R0—margins microscopically negative

FIGURES



*Indicates only a partial year (January to September)