

Hybrid Minimally-invasive Esophagectomy for Esophageal Cancer: Clinical and Oncological Outcomes

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Abstract. *Background/Aim:* Esophagectomy is a major surgical procedure associated with a significant risk of morbidity and mortality that has traditionally been performed by an open approach. Although minimally invasive procedures for benign esophageal disease have been widely accepted worldwide, they have not yet been established for the treatment of malignancy. *Patients and Methods:* A total of 137 consecutive hybrid esophagectomies for cancer were performed by the same surgical team. Surgical approach included either 2-stage or 3-stage hybrid minimally-invasive esophagectomy. *Results:* Median age of patients was 64 years. Respiratory complication and anastomotic leak rates were 16.78% and 9.48%, respectively. Median follow-up was 48 months with median overall survival and disease free survival were 58 and 48 months, respectively. *Conclusion:* Advances in minimally invasive surgery can benefit patients with esophageal cancer, mainly by reducing post-operative respiratory complications. Hybrid esophagectomy is safe and feasible in tertiary esophago-gastric centers with vast expertise that can lead to improved clinical and oncological outcomes.

Esophageal cancer is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide with annually increasing incidence (1). Moreover, it has been associated with an overall 5-year survival rate of 15-20%. Esophagectomy is the mainstay in curative treatment for local and loco-regional disease. It is often combined with neoadjuvant or perioperative chemotherapy with or without

radiotherapy. However, esophageal surgery has been shown to have high rates of peri-operative mortality and morbidity (2).

Surgical treatment of esophageal cancer has been established through either an open transhiatal, transthoracic (2-stage or Ivor-Lewis) or 3-stage (McKeown) procedure. In certain circumstances, the surgical approach is dictated by cancer location or histologic type. Patients with adenocarcinoma of the distal esophagus or esophago-gastric junction (Siewert type I-II) are in the vast majority being treated with 2-stage esophagectomy and intrathoracic esophago-gastric anastomosis. In patients with cancer of the mid-esophagus, which are mainly squamous cell carcinomas more proximal esophageal resection is needed and 3-stage esophagectomy with cervical esophago-gastric anastomosis is performed. However, not infrequently, the type of esophageal resection performed is, to some degree, one of a personal preference and different surgical approaches are utilized between different surgeons (3).

Minimally invasive esophagectomy was introduced in the early 90's, with the aim of reducing the major respiratory complications associated with thoracotomy procedures (4). There have been numerous approaches developed throughout the years and applied in the treatment course of esophageal cancer. Since the first laparoscopic procedure, there has been a steady increase in advanced minimally invasive surgery. Implementation of these procedures requires different and new skills for the surgeons.

In the present study, we report our initial experience of hybrid minimally-invasive, either 2-stage or 3-stage esophagectomy, performed for esophageal cancer. Hybrid esophagectomy is safe and feasible in tertiary esophago-gastric centers, with excellent clinical and oncological outcomes.

Patients and Methods

This is a retrospective analysis of prospectively collected data regarding n=137 consecutive patients that underwent hybrid 2-stage or 3-stage esophagectomy for cancer by one surgical team in a high-

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volume tertiary center over a 36-month period. All cases treated, were for mid-esophageal, distal esophageal or esophago-gastric junction (EGJ) tumors (Siewert Type I and II), and with hybrid Ivor-Lewis esophagectomy with a laparoscopic phase followed by right posterolateral thoracotomy or hybrid McKeown esophagectomy (thoracotomy/laparoscopy/left neck).

Surgical procedures

Hybrid 2-stage minimally-invasive esophagectomy. Surgical procedure refers to a two-stage Ivor-Lewis procedure (laparoscopic abdominal phase followed by right thoracotomy phase), with an intrathoracic esophago-gastric anastomosis. Standard two-field lymph node dissection was performed in all cases. A split-leg with a steep reverse Trendelenburg position was used.

Mobilization of the stomach *via* division of the gastrocolic and gastrosplenic ligaments 3-4 cm outside the gastroepiploic arcade was performed. The pars flaccida was divided close to the liver and the hiatus mobilized, by removing part of the diaphragmatic crura and lower mediastinal pleura bilaterally, pericardial fat anteriorly and para-aortic fat posteriorly. A D2 abdominal lymphadenectomy including left gastric, celiac, splenic, and common hepatic nodes was part of the standard procedure. A 4-5cm wide gastric conduit was formed with the use of the iDrive™ ultra powered stapling system (Medtronic, Minneapolis, MN, USA) with purple cartridges. The last 2 cm of the conduit at the gastric fundus remained uncut, to facilitate conduit relocation into the right hemithorax during the thoracic phase of the procedure.

Following the laparoscopic phase, the patient was placed on a left lateral decubitus position and *via* a 15 cm posterolateral thoracotomy through the fifth intercostal space, thoracic access was gained. Esophageal mobilization beginning 2 cm above the azygos vein and towards the esophago-gastric junction (EGJ), where it joined the abdominal hiatal dissection, was achieved *en-bloc* with mid and lower mediastinal lymphadenectomy (encompassing peri-esophageal, para-aortic, diaphragmatic, pericardial and subcarinal lymph nodes). The esophagus was transected at the level of the azygos vein and the gastric conduit was brought to the chest. The remaining attached gastric fundus was stapler-transected and the specimen was extracted. An esophageal purse-string with 3/0 Prolene suture was constructed and the anvil placed intraluminally. A 3 cm, along the long axis of the conduit, anterior gastrotomy was performed half way between the stapler line and the greater curvature. The CDH circular stapler (Ethicon, Cornelia, GA, USA) was inserted through the gastrotomy and through the posterior conduit wall an end-to-side esophago-gastric anastomosis was constructed; the stapler size (25 or 29 mm) was adjusted according to the internal esophageal diameter. Once the nasogastric tube was placed across the anastomosis under direct vision, the anterior gastrotomy was approximated with a continuous 3/0 polydioxanone (PDS, Ethicon) extramucosal suture.

The tip of the nasogastric tube was left at this point at the level of esophago-gastric anastomosis to facilitate an anastomosis leak test with methylene blue. Following that and once the anastomotic integrity was established, the nasogastric tube was further advanced 5-10 cm into the gastric conduit. A 24 Fr chest drain was placed and the thoracotomy was closed in layers.

Hybrid 3-stage minimally-invasive esophagectomy (McKeown). This surgical procedure refers to standard 3-stage esophagectomy procedure, with open right thoracotomy, followed by laparoscopic

abdominal phase, as presented in the hybrid 2-stage esophagectomy (Ivor-Lewis procedure), and cervical anastomosis during the final cervical phase of the approach.

The first stage was started with a right posterolateral thoracotomy. Once the right hemithorax was entered, the azygos vein arch was dissected and divided between Hem-o-lok clips. The mediastinal pleura overlying the esophagus was then divided. The thoracic esophagus, along with the periesophageal tissue and mediastinal lymph-nodes, was circumferentially mobilized from the hiatus to the thoracic inlet. Dissection of the mediastinal pleura was performed on both sides of the esophagus starting between the vagal trunk and the right main bronchus. This allowed *en-bloc* lymphadenectomy including the subcarinal ones with preservation of the cardiac and pulmonary vagal branches in most circumstances. The thoracic duct was identified and ligated with a Hem-o-lok clip anterior to the descending thoracic aorta, 2cm above the level of the hiatus. Extended 2-field mediastinal lymphadenectomy was performed in every case, and the resected lymph nodes included left and right recurrent laryngeal, paratracheal, subcarinal, left and right bronchial, lower posterior mediastinum, para-aortic, and para-esophageal lymph nodes. The chest cavity was inspected and hemostasis was verified. A 24 Fr chest tube was placed routinely.

Once esophageal mobilization was performed, the patient was turned supine and a simultaneous abdominal and neck approach by two surgical teams was instigated. The abdominal phase was performed laparoscopically, as presented in the 2-stage hybrid esophagectomy.

During the cervical phase, a 5 cm oblique incision was made at the anterior border of the left sternomastoid muscle. The cervical esophagus was mobilized to permit communication with the right chest, taking care to preserve the recurrent laryngeal nerves. The cervical esophagus was divided 2 cm distal to the cricopharyngeus muscle. An umbilical tape was stitched to the distal end of the esophagus (specimen) so as to maintain the posterior mediastinal route after specimen retrieval through the abdomen. The anastomosis was performed with 4/0 Polydioxanone (PDS) Gambee sutures in an interrupted manner.

Histopathology. Pathological staging was reported according to the seventh edition of the American Joint Committee on Cancer TNM system (5). Currently, there is discrepancy between the definition of surgical clearance and circumferential resection margin (CRM) involvement in esophageal cancer provided by the Royal College of Pathologists (RCP) (6). Therefore, the CRM status was reported according to RCP criteria.

Statistical analysis. All of the statistical analysis was performed based on the curative intention of surgical procedures. All continuous variables are reported as means and medians with their corresponding standard deviations and ranges. Kaplan–Meier analysis survival was used to estimate the time-to-event points. The survival end points were presented with their respective median values and rate at specific time points, with 95% Confidence Interval. Statistical analysis was performed using SPSS software version 20.0 (IBM, Armonk, NY, USA).

Results

From January 1st 2013 until August 31st 2017, 137 consecutive esophagectomies for cancer were performed from the same surgical team. Among them, 117 were male

Table I. Epidemiological and clinical characteristics of the study population.

Characteristics	Patients (n=137)
Median age (range)	64 years (range=32-80 years)
Gender	
Male	n=117 (85.41%)
Female	n=20 (14.59%)
Neoadjuvant chemotherapy	n=108 (78.3%)
Surgical approach	
Hybrid 2-stage esophagectomy	n=126 (91.97%)
Hybrid 3-stage esophagectomy	n=11 (8.02%)
Pre-operative tumor differentiation	
Poor	n=75 (54.74%)
Moderate	n=48 (35.03%)
Well-differentiated	n=14 (10.21%)
Pre-operative stenting	n=17 (12.4%)
Feeding jejunostomy	n=45 (32.84%)
Mean operative time	360 min (range=270-430 min)
Median length of stay	16 days (range=8-70 days)
Post-operative complications	
Wound infection	n=7 (5.1%)
Chest infection	n=23 (16.78%)
Pleural effusion	n=10 (9.25%)
Atrial fibrillation	n=3 (2.18%)
Vocal cord palsy	n=3 (2.18%)
Hiatal hernia	n=4 (2.91%)
Chyle leak	n=6 (4.73%)
Anastomotic leak	n=13 (9.48%)
30-day mortality	n=4 (2.91%)
90-day mortality	n=7 (5.1%)

Table II. Histopathological outcomes.

Histological type	
Adenocarcinoma	n=126 (91.97%)
Squamous carcinoma	n=11 (8.02%)
Tumor T-status	
HGD	n=4 (2.91%)
pTis	n=6 (4.37%)
pT1a	n=8 (5.83%)
pT1b	n=13 (9.48%)
pT2	n=30 (21.89%)
pT3	n=60 (43.79%)
pT4	n=16 (11.67%)
Tumor N-status	
N0	n=63 (45.98%)
N1	n=30 (21.89%)
N2	n=20 (14.59%)
N3	n=24 (17.5%)
Lymphovascular invasion	n=57 (41.6%)
Perineural invasion	n=49 (35.76%)
Median number of lymph-nodes extracted	n=29 (range=11-60)
R-status*	
R0	n=121 (88.32%)
R1	n=16 (11.67%)
CRM*	
Negative	n=128 (93.43%)
Median CRM	3 mm (range=0-15 mm)
Adjuvant therapy	n=58 (53.7%)
Chemotherapy	n=51 (87.93%)
Radiotherapy	n=7 (12.06%)

*According to Royal College of Pathologists (RCP); CRM: circumferential resection margin; HGD: high-grade-dysplasia.

patients (85.41%) and 20 females (14.59%). Median age was 64 years (range=32-80 years). Neo-adjuvant chemotherapy was given to 108 (78.83%). Epidemiological and clinical characteristics of the study population are shown in Table I.

The preoperative chemotherapy regimen was a combination of intravenous epirubicin and cisplatin with oral capecitabine (ECX) in 80 patients (74.07%) and intravenous epirubicin and oxaliplatin with oral capecitabine (EOX) in 28 patients (25.92%). Of the patients who had neo-adjuvant chemotherapy, 80 (74.07%) completed all three cycles. According to RECIST criteria (7), partial response was observed in 75 patients (69.44%), stable disease in 25 (23.14%) and progressive disease (without evidence of distant metastasis) in 8 (7.4%).

Operative approach was hybrid 2-stage esophagectomy in 126 patients (91.98%), and hybrid 3-stage esophagectomy in 11 cases (8.02%). Of the 108 patients who received neo-adjuvant chemotherapy, 58 (53.7%) had adjuvant treatment (chemotherapy for 51 and radiotherapy for 7).

According to D. Low *et al.*, we encountered an overall anastomotic leak rate of 9.48% (n=13); 3 (23%) type I anastomotic leaks requiring no intervention, 9 (69.23%) type II leaks were treated with endoscopic stent insertion, whereas

1 (7.69%) type III leak required reoperation (8). Furthermore, 6 (4.37%) cases were complicated with chyle leak (n=4 type IA and n=2 type IIA), 3 (2.18%) with vocal cord palsy (type IA), 4 (2.91%) with hiatal hernias, 23 (16.78%) cases with severe chest infections (pneumonia) and 10 (9.25%) with pleural effusion requiring drainage (8).

Thirty-day mortality was 2.91% (n=4) and 90-day mortality was 5.1% (n=7). From these patients, 3 patients died due to respiratory failure and chest infection, 1 patient developed a broncho-esophageal fistula, 1 patient died due to cardiac arrest in ICU, and 2 patients died of progressive metastatic disease following discharge.

Twenty-eight (20.43%) patients had adenocarcinoma of the distal esophagus and 98 (71.5%) had adenocarcinoma of the esophago-gastric junction. Of the latter group, 33 (33.67%) were of Siewert type I, and the remaining 65 (66.32%) were of Siewert type II. Eleven patients had mid-esophagus squamous cell carcinoma.

Tumor status was pT0 in 4 (2.91%), pTis in 6 (4.37%), pT1a in 8 (5.83%), pT1b in 13 (9.48%), pT2 in 30 (21.89%), pT3 in 60 (43.79%) and pT4 in 16 (11.67%) patients. Lymph-node status was pN0 in 63 (45.98%), pN1 in 30

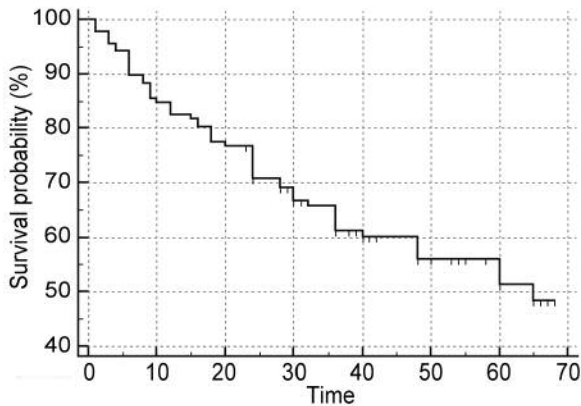


Figure 1. Kaplan–Meier curve of the estimated overall survival.

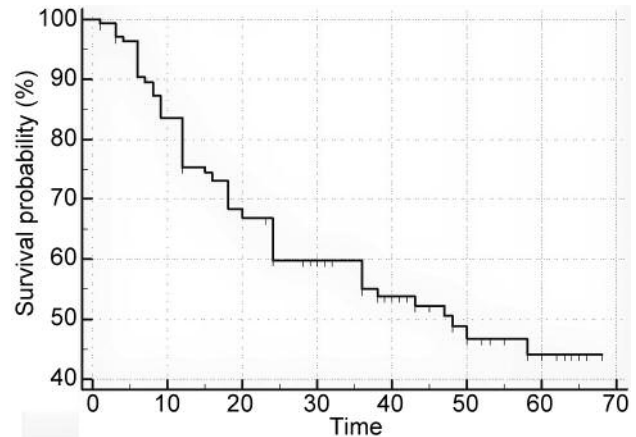


Figure 2. Kaplan–Meier curve for the estimated disease-free survival.

(21.89%), pN2 in 20 (14.59%) and pN3 in 24 (17.5%) patients. The median number of lymph nodes removed was 29 (range=11-60).

R0 was achieved in 121 patients (88.32%) according to the Royal College of Pathologists (RCP). Circumferential resection margin (CRM) was negative in 118 patients (86.13%) according to Royal College of Pathologists (6). The median CRM of patients was 3 mm (range=0-15 mm). The CRM coincided with the esophago-gastric junction in 51 patients (37.22%). The complete details of the final histopathological results are shown in Table II.

All patients went to intensive care (ICU) postoperatively and were extubated within 24 hours. Median length of stay (LOS) was 16 days (range=8-70 days). Mean operating time was 360 min (range=270-430 min), with no blood loss over 500 ml noted in any case.

The median follow-up time, assessed by the means of reverse Kaplan–Meier analysis, was 48 months (95%CI=42-54). Among the 137 patients that underwent hybrid minimally invasive esophagectomy, 58 (42.34%) died during the follow-up period. The median overall survival was 58 months (95%CI=52-64) (Figure 1), while disease free survival was 48 months (95%CI=36-58) (Figure 2). All data regarding clinical outcomes are presented in Table III.

Discussion

The aim of this study was to describe the implementation of minimally-invasive techniques and to present the clinical and oncological outcomes of 137 consecutive patients that underwent hybrid minimally-invasive esophagectomy for cancer over the course of three years.

It is well established, that the surgical approach that is chosen has a significant impact both on peri-operative and

Table III. Clinical outcomes.

Median follow-up	n=48 months (95%CI=42-54)
Median overall survival	n=58 months (95%CI=52-64)
Disease-free survival	n=48 months (95%CI=36-58)

post-operative complications; transthoracic esophagectomy is more prone to respiratory complications, while neck dissection and superior mediastinal dissection during 3-stage esophagectomy carry an important risk for recurrent laryngeal nerve injury. In addition, anastomotic leak and stricture have a higher incidence following cervical anastomosis. However, anastomotic leakage after intrathoracic anastomosis can be fatal, mainly due to mediastinitis and sepsis that it is related to.

Minimally invasive esophagectomy was first described by Cushiery *et al.* in 1992 (4), but it was not until 1997 that it gained popularity with Swanstrom (9). Their method included total esophagectomy, combining a laparoscopic transhiatal phase and a cervical approach to retrieve the esophagus and perform the esophago-gastric anastomosis. Following that, Lucetich and colleagues in 1998, were amongst the first to report thoracoscopic esophageal mobilization (10), resulting in better peri-operative outcomes in their series of 222 patients (11). In 2006, Lucetich *et al.* presented their results of high intra-thoracic anastomosis performed *via* mini-thoracotomy or thoracoscopic approach instead of their initial approach of thoracoscopic esophageal mobilization and cervical anastomosis. They concluded that minimally invasive 2-stage esophagectomy is safe and feasible, with excellent peri-operative results regarding anastomotic leakage, respiratory complications and injury of

the recurrent laryngeal nerves compared to their earliest publications about minimally invasive esophagectomy (12). Esophago-gastric anastomosis is one of the deciding factors of an esophagectomy. Over the years many approaches have been proposed for the construction of anastomosis, with well-established techniques in cervical or intrathoracic esophago-gastric ones. With the implementation of minimally invasive techniques in esophageal surgery, this major issue was revived. Ben-David *et al.* have reported adequate results in intrathoracic stapled esophago-gastric anastomosis regarding anastomotic leak and stricture rates (13). On the contrary, Nguyen *et al.* have presented relatively higher rates of anastomotic leak and stricturing when performing esophago-gastric anastomosis with circular 25 mm stapler (14).

Our results parallel those of recently published studies that conclude that hybrid minimally invasive esophagectomy resulted in a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complications, than open esophagectomy, without compromising overall and disease-free survival (15).

The strengths of our study include that all the procedures were performed from the same surgical team, experienced in upper gastrointestinal and esophageal surgery, with a standardized surgical technique. In addition, the study cohort of 137 patients with esophageal cancer is adequate and does not have selection bias, as it was offered to all-comers. Study limitations on the other hand, include the retrospective study type, and while no patients were lost in the follow-up, 5-year follow up period is not completed in the patients treated after June 2014.

The use of minimally-invasive techniques in esophageal surgery is widely increasing; improved outcomes have been reported in many related publications (16, 17). In a recent report evaluating the trends in implementation and outcomes of minimally-invasive esophagectomy versus open esophagectomy, Lazzarino *et al.* (17) presented a trend toward better 1-year survival in patients undergoing minimally-invasive esophagectomy. Following that, a systematic review of more than 1100 patients evaluating minimally-invasive and open esophagectomy, showed that minimally-invasive esophagectomy was associated with decreased morbidity rates as well as shorter length of hospital stay compared to open (18).

Implementation of minimally-invasive techniques in esophageal surgery is widely adopted, with favorable clinical and oncological outcomes. A significant decrease in post-operative morbidity due to better patient selection, improved perioperative care and alteration of surgical approach in high-volume centers has been reported in the published literature. Herein, we present our initial experience of hybrid minimally invasive esophagectomy with 2-field or extended 2-field lymphadenectomy in patients with resectable intra-

thoracic or intra-abdominal esophageal and esophago-gastric junction cancer. Potential advantages of this approach include lower post-operative respiratory complication rate, higher lymph node yield with improved oncological outcomes. Hybrid 2-stage as well as 3-stage esophagectomy has proven safe and feasible in large volume tertiary centers and can lead to a paradigm shift.

Conflicts of Interest

All of the Authors declare no potential conflict of interest. There were no sponsorship or funding arrangements related to this research.

Authors' Contributions

Spyridon Davakis: drafting of manuscript and analysis and interpretation of data; Athanasios Syllaios: analysis and interpretation of data, drafting of manuscript; Elias Sdralis: drafting of manuscript and analysis and interpretation of data; Bruno Lorenzi: acquisition of data, drafting of manuscript; Alexandros Charalabopoulos: study conception and design, acquisition of data and drafting of manuscript.

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