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Minimally Invasive Esophagectomy for Esophageal Cancer: Techniques and Outcomes

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Rezumat

Esofagectomia minim-invazivă în cancerul esofagian: tehnici și rezultate

În ciuda progreselor recente în diagnosticarea, tratamentul chirurgical și terapia neoadjuvantă, pacienții cu cancer esofagian prezintă un prognostic prost cu rate de supraviețuire la 5 ani cuprinse între 5-15%. Esofagectomia este tratamentul standard pentru cancerul esofagian rezecabil, dar doar o treime din pacienți sunt considerați candidați pentru tratament. Tehnici minim-invazive au fost încercate în vederea îmbunătățirii rezultatelor postoperatorii aferente unei proceduri cu morbiditate și mortalitate postoperatorie atât de mari. Scopul acestei lucrări este de a analiza tehnicile de esofagectomie minim-invazivă (EMI) în cazul carcinoamelor esofagiene în stadiu incipient. EMI este în continuare corelată cu o serie heterogenă de studii pe diferite tehnici. Comparativ cu procedurile de esofagectomie prin chirurgie deschisă, EMI prezintă morbiditate scăzută cu incidență scăzută global a infecțiilor pulmonare nosocomiale și durată mai scurtă de internare la terapie intensivă. În plus, tehnicile de EMI oferă o calitate a vieții mai bună decât procedurile deschise, cu recuperare postoperatorie mai rapidă.

Cuvinte cheie: laparoscopie, esofagectomie, cancer esofagian

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Abstract

Despite recent improvements in diagnosis, surgical treatment and neo-adjuvant therapy, patients with esophageal cancer have poor prognosis with overall 5-year survival rates of 5-15%. Esophagectomy is the standard treatment for resectable esophageal cancer, but only one third of patients are considered candidates for cure. Minimally invasive techniques have been attempted to improve the postoperative outcomes in such a surgical procedure with high postoperative morbidity and mortality. The purpose of this review is to analyze the minimally invasive esophagectomy (MIE) techniques in the early-stage esophageal carcinoma. MIE is still crowed with heterogeneous studies with several different techniques. MIE comparing to open esophagectomy procedures have less morbidity with less overall in-hospital incidence of pulmonary infections and shorter duration of ICU admission. In addition, MIE techniques preserve the quality of life better than the open procedures, with faster postoperative recovery.

Key words: laparoscopy, esophagectomy, esophageal cancer

Introduction

The incidence of esophageal cancer in the Western world has risen sixfold the past 25 years and currently the disease is the sixth leading cause of death worldwide. (1) Despite recent improvements in diagnosis, surgical treatment and neo-adjuvant therapy, the prognosis of patients with esophageal cancer remains poor, with overall 5-year survival rates of only 5%-15%. (2) Esophagectomy is the standard treatment for those patients who present with resectable esophageal cancer,

but it offers a limited (25%-35%) chance of cure. (2) Surgical resection with radical lymphadenectomy, usually after neoadjuvant chemotherapy or chemo-radiotherapy, remains the only curative option for resectable esophageal cancer. (3) The 5-year survival rate for patients resected with a curative intent is approximately 40%. (4) However, despite advances in surgical and perioperative management, postoperative morbidity, especially pulmonary complications, remains high and is reported between 30% and 50%, with a significant postoperative mortality between 2% and 10%. (4)

MIE has been attempted during the last decade with the aim of improving the postoperative outcomes without compromising oncological outcomes. In 1991, Dallemagne (5) introduced the right thoracoscopic approach for esophageal cancer with total lung block, thereby mimicking the conventional approach. Initial reports showed a high conversion rate to thoracotomy of 10% to 17% and a high respiratory morbidity of 17% to 42%. (6,7) Searching for reduction of the conversion rate and the respiratory infection rate, Cuschieri et al (8) designed the thoracoscopic approach in prone decubitus position so that a total collapse of the lung was no longer necessary for dissecting the esophagus and thereby possibly reducing the rate of respiratory infections. Many institutions have reported their experiences in the adoption and refinement of MIE for benign and malignant diseases of the esophagus. (9) Current surgical approach in esophageal cancer has embraced new minimal invasive techniques. The aim of this review is to analyze the literature to-date and the controversies about MIE.

Indications for minimally invasive esophageal resection

Benign esophageal diseases are an infrequent indication for esophageal resection. Nevertheless, important caustic and peptic stenosis not suitable for treatment by balloon dilatation may finally be considered indications for resection. End-stage motility diseases of the esophagus like achalasia and Chagas's disease with megaesophagus and the presence of multiple esophageal epiphrenic diverticula may also be an indication for resection. Also, borderline high grade dysplasia of the Barrett's esophagus (BE) may be a good indication for resection by minimally invasive techniques. (10)

On the other hand, cancer of the esophagus is the most frequent indication for resection. Once diagnosed, it is important to establish a good preoperative assessment of the resectability. Surgery is considered when the tumor is staged as cT1-3 N0-1 M0 (clinical stage according to the 7th edition of the TNM classification). Moreover, treatment of the esophageal cancer needs a multidisciplinary approach and usually patients with a locally advanced cancer will be treated by neoadjuvant chemoradiation, making surgery perhaps more difficult. All operable cancers in any location can be approached by minimally invasive surgery. (10) Indications are the same as for open surgery, as far as the stage of disease is concerned, although early T stage tumors were best candidates for thoracoscopic approach in some institutes, especially when they started employing the procedure. (11) Law et al (12) reported that the advantages of thoracoscopic surgery over open surgery were not obtained in patients with increased operative risk, such as liver cirrhosis or other cormobidities. However, Osugi et al (13) set some limitations of thoracoscopic esophagectomy in patients who received preoperative anticancer treatment, especially radiation because this therapy may obscure the microanatomy, which can only be confirmed under the magnification of a scopic surgery. Others, such as Higashino et al and Miyazaki et al indicate the procedure for such medically invaded patient to reduce surgical invasiveness. (13) This is because the Japan Esophageal Society supports the need of a three field lymphadenectomy and that the cervical and upper mediastinal lymph nodes, in particular, the recurrent nerve chain nodes are defined to be regional. (14)

In particular, the indications of thoracoscopic esophagectomy for esophageal cancer are listed in *Table 1*.

Minimally invasive esophagectomy techniques

Currently esophagectomy remains the standard treatment for patients with esophageal cancer. The 5-year survival rate for esophagectomy in early esophageal adenocarcinoma approaches 90%. (15,16) Several studies have indicated that multicentric disease may be present throughout the Barrett's mucosa in about 50% of patients with early Barrett's related cancer, therefore removal of the entire area with intestinal metaplasia in the distal esophagus should be mandatory for all patients in order to avoid recurrences. (17,18) For patients with submucosal invasion, esophagectomy with appropriate lymphadenectomy is currently the standard of care. This is because the muscularis mucosa is an important anatomic boundary that affects the likelihood of lymph node metastases. One of the major disadvantages of esophagectomy is the substantial risk that it carries; the overall postoperative complication rate ranges between 30% and 80% with a reported mortality rate of 5% in high-volume centers. (16) Options for a surgical approach include transthoracic esophagectomy (TTE), transhiatal esophagectomy (THE), and a variety of approaches to minimally invasive esophagectomy (MIE). Several minimally invasive approaches for esophagectomy have been described: total transhiatal laparoscopic approach, esophagectomy using right thoracoscopy, combined laparoscopic and right thoracoscopic esophagectomy, esophageal resection through mediastinoscopy, robot-assisted esophagectomy and hybrid techniques. There are theoretical benefits to these minimally invasive approaches, such as less blood loss and shorter intensive care unit and hospital stay, although they are countered by their complexity and increased operating time. MIE for cancer avoiding the thoracotomy and laparotomy can reduce the amount of trauma of the required surgery with the same onco-

Table 1. *Indications of thoracoscopic esophagectomy for esophageal cancer*

1.	Absence of extensive pleura adhesions.
2.	Absence of contiguous tumor spread to adjacent structures.
3.	Pulmonary function capable of sustaining single lung ventilation.
4.	Absence of a concomitant serious medical condition, such as liver cirrhosis.
5.	Patient preference for the procedure.
6.	Patient without anticancer treatment?

logical value. (19) This will imply a reduction of the postoperative morbidity, a shortening of the recovery time and an increase of quality of life. Evidence of the short term benefits of minimally invasive surgery over open procedures with similar oncological outcome is accumulating. Less perioperative complications, shorter hospital stay and faster postoperative recovery appear to be the main advantages.

Laparoscopic transhiatal esophagectomy

The transhiatal approach for esophagectomy was initially described by Denk in 1913, but was later popularized by Orringer. (20) This method has gained popularity in recent years because it avoids the additional morbidity associated with thoracotomy. Performance of transhiatal esophagectomy using a laparoscopic approach minimizes surgical trauma by avoiding a formal laparotomy, thus leading to decreased morbidity and accelerated postoperative recovery. DePaula et al (21) were the first to demonstrate the feasibility of laparoscopic esophagectomy in a series of 12 patients who underwent laparoscopic transhiatal esophagectomy, 2 of these patients had malignant esophageal tumors. Transhiatal surgery seems best suited to early stage disease including multifocal high grade dysplasia in patients with very long Barrett's segments. (15) Especially, for adenocarcinoma of the esophagogastic juction and lower third of esophagus most surgeons accept the need for an adequate abdominal lymphadenectomy and the laparoscopic transhiatal esophagectomy as an option. (15) The anastomosis can be done either intrathoracic or a cervical esophago-gastric anastomosis is an alternative solution.

Thoracoscopic and laparascopic esophagectomy with cervical or intrathoracic anastomosis

From a historical point of view, Dallemagne et al described in 1992 the first combined thoracoscopic and laparoscopic approach for esophageal resection for cancer with reconstruction by means of a gastric conduit anastomosed to the neck (22) and reported the outcome of the first twelve patients operated on in this way during the period between June 1991 to July 1992. (5) In the same year, Azagra et al. (6) and Cuschieri et al. (23) described their initial experience with a small series of patients with esophageal cancer in whom the esophagus resection and mediastinal lymphadenectomy was performed through a right thoracoscopic approach. The rest of operation was completed through a laparotomy and consequent cervical approach. Mean operative times for the thoracoscopic approach were between three and four hours. Gossot et al., performed the same thoracoscopic esophageal resection in 15 patients in 1993, had a 20% conversion rate (large tumor in one patient and incomplete lung collapse in another two) and significant postoperative pulmonary complications in another two patients. (7) The philosophy for the development of this minimally invasive approach was to obtain the same oncological outcome as the conventional procedure, but with all postoperative advantages of the minimally invasive approach.

The thoracoscopic approach can be done either with the minimally invasive Ivor Lewis esophagectomy, or with the minimally invasive three-stage operation. Most surgeons use these techniques for squamous carcinomas of the middle and upper third of the esophagus, where adequate lymphadenectomy in the abdomen and mediastinum seems more reasonable. (15) For adenocarcinonas, an adequate abdominal lymphadenectomy is required, as the predominant route of lymphatic spread in lower third tumors is in a caudal direction. The extent of the mediastinal lymphadenectomy, in particularly in the upper half of the mediastinum, remains unclear, although Japanese surgeons routinely do three-field lymphadenectomy (14,15). The most widely practiced operation is the two-phase Ivor Lewis minimally invasive procedure and some surgeons favor a third stage with cervical incision to create the anastomosis at this level so as to gain adequate clearance in proximal tumors.

Esophageal resection through Mediastinoscopy. Video-assisted mediastinoscopic transhiatal esophagectomy

The basic uses of mediastinoscopy include mediastinal mass biopsy and lymph node biopsy for the diagnosis. With the development of endoscopic technology, the applicative area of mediastinoscopy expanded. By now video-assisted mediastinoscopy can be used for the separation of the esophageal tumor. Esophagectomy via mediastinoscopy was firstly reported by Buess in 1990. The advantage of video-assisted mediastinoscopic transhiatal esophagectomy is not only to avoid thoracotomy and reduce bleeding compared with traditional transhiatal esophagectomy, but also to resect mediastinal lymph node thoroughly. Also, laparoscopic techniques have developed rapidly in recent years, and can be used to mobilize the stomach and to mobilize the lower esophagus via hiatus. A combination of mediastinoscopy and laparoscopy can be used for complete esophagectomy and reconstruction of digestive tract. Mediastinoscopy combined with laparoscopic surgery had been reported by Bonavina et al in 2004 (24). According to this technique video-assisted mediastinoscopy dissected the middle and upper thoracic esophagus under direct vision while laparoscopy dissected the lower esophagus. (25,26)

Robot-assisted procedures

The first case description of thoracoscopic esophagectomy aided by robotic system was published in 2004 by Kernstine (27) and colleagues who used the Da Vinci Robotic system (Intuitive Surgical, Inc, Sunnyvale, Cal.). Their series consisted of three consecutive groups, each combining the robot-assisted thoracoscopic procedure with either open abdominal surgery, laparoscopy, or robot-assisted laparoscopy. From that period and on many have introduced the robot-assisted esophagectomy with encouraging results. (28,29) The operation is performed in 2 stages first in the left lateral position and then supinely.

There is a case report of a robotic esophagectomy by Horgan S et al. (30) The esophagus was removed in a transhiatal fashion. No wide nodal resection was performed because the robotic arms were too short to reach the carina, requiring the peritracheal portion of the esophagus to be removed through the neck incision and thoracic inlet. Recently a team from India (29) published their experience with robotic transthoracic

esophagectomy in 32 patients with esophageal cancer, with the abdominal phase done laparoscopically. The results were encouraging. A team from Netherlands (28) introduced the robot-assisted esophagectomy for the intrathoracic phase and they found the robotic system less suitable for the abdominal phase, requiring manoeuvres with large amplitude leading to collisions of the robotic arms. They performed the abdominal phase by conventional laparoscopy reducing the time of operation by nearly 4 hours. The main disadvantage of the robot-assisted method is the time requiring, although the magnification, the 3-dimensional view, and the 7 degrees of freedom led to decreased blood loss and better dissection. (29)

Hybrid techniques

In hybrid procedures at least one of the approaches being done via either laparoscopy or thoracoscopy. In that kind of techniques belongs the hand-assisted procedure.

To decrease the complexity of total minimally invasive esophagectomy while still conserving the benefits of the approach, some surgeons began performing esophagectomy using a laparoscopic-assisted transhiatal approach (LA-THE). (16) This strategy offers the advantages of the open transhiatal technique, such as decreased cardiopulmonary morbidity. In addition, this technique offers direct demonstration of the mediastinum using a camera to allow the creation of a well-developed surgical plane with potentially high-yield harvesting of the lymph nodes. Furthermore, with this LA-THE approach, the learning curve should not be as steep as that for the total minimally invasive esophagectomy – which is beneficial to the patient.

Another approach is the combining laparoscopy and right thoracotomy operation (31), which can be advantageous in regards to respiratory function. Osugi H. et al published their series of 75 patients who underwent three-level lymphadenectomy with the thoracic phase be done with a mini thoracotomy of 5cm and 4 additional trocars. They concluded that mini thoracotomy was essential to perform the procedure safely and effectively. (13, 32)

Finally, the MIRO trial (4), a prospective multicenter controlled randomised phase III trial, compared the laparoscopic gastric mobilization and open thoracotomy (Hybrid technique) with the open esophagectomy (with open gastric mobilization and thoracotomy) in patients with thoracic esophageal cancer who underwent esophagectomy through the abdominal and right thoracic approach (Ivor-Lewis procedure). The conclusion was that the hybrid operation may provide a significant decrease in major postoperative complications without leading to any negative impact on oncological outcomes based on: (i) the lower expected rate of pulmonary complications due to the less invasive nature of the procedure and reduced deterioration of the ventilatory mechanisms compared to the open procedure, and (ii) the ease of performance and reproducibility at specialized and non-specialized centres. (4) The procedure can decrease major postoperative morbidity without compromising oncological outcomes and can be considered as a simple, safe, reproducible and effective technique worldwide (4).

Discussion

Surgery on cancer of the esophagus is considered to be one of the most extensive and traumatic oncological surgical procedures. Open resection not only involves a long operation time and large incisions but also necessitates post-operative care in the intensive care unit, a long in-hospital recovery with decreased quality of life and carries a significant risk of morbidity and death. MIE can reduce the post-operative morbidity, in particular the respiratory complications which are most encountered. Different landmark studies have reported significantly low pulmonary complications rates using the minimally invasive transthoracic approach. Palanivelu et al. reported in their minimally invasive series of 130 patients in prone-position, 2.3% pulmonary complications (33), whereas Luketich et al. reported in their series of 222 patients in left lateral decubitus MIE, 18% pulmonary complications. (34) In contrast, Hulscher et al. observed 57% pulmonary complications in patients undergoing the traditional three-stage transthoracic esophagectomy. (35) Furthermore, median length of Intensive Care Unit (ICU) stay was one day in the series of Palanivelu and Luketich, whereas in the traditional series of Hulscher the ICU stay was 6 days. Review papers show a median length of intensive care unit stay of 2-5 days, and a median length of hospital stay of 9-18 days after MIE. (36,37)

Concretely, in the report of Luketich et al. (34), operative mortality was 1.4%, morbidity included anastomotic leak rate of 11.7%, pneumonia incidence of 7.7%, and recurrent laryngeal nerve injury with vocal cord palsy rate of 3.6%. Their preferred and most commonly employed approach was the combined right thoracoscopic and laparoscopic THE. The same group later described their early experience with minimally invasive Ivor Lewis Esophagectomy (ILE) in 50 patients from 2002 to 2005 with an operative mortality and leak rate of 6% each. (38) Rajan et al. also published a large series of 463 patients in India who underwent minimally invasive esophagectomy. Operative mortality was 0.9%, and overall morbidity was 16%. (39) Similarly, Nguyen and colleagues reported a series of 104 MIE procedures performed between 1998 and 2007. Most procedures were minimally invasive Transhiatal Esophagectomies (THE) or Ivor Lewis Esophagectomies (ILE). Major complication rate was 12.5%, and minor complication rate was 15.4%. Anastomotic leak rate was 9.6%, and operative mortality was 2.9 %. (40) Consequently, Ben-Davis et al. (41) reported their results in 105 consecutive patients who underwent MIE. The mortality was 1% (1/105), and morbidity included 7% transient left recurrent laryngeal nerve injury, 9% pneumonia, 1% wound infection, and 4% anastomotic leak rate. (41)

Gemmill and McCulloch published one of the earliest systematic reviews of minimally invasive operations for esophageal and gastric cancer based on an electronic search of the literature from 1997 to 2007. (36) The operations were any combination of thoracoscopy or thoracotomy with laparoscopy, hand-assisted laparoscopy, or laparotomy (i.e., MIE or hybrid MIE). For MIE or hybrid MIE, 30-day mortality was 2.3%,

combined major and minor morbidity was 46.2%, anastomotic leak rate was 7.7%, and respiratory tract infection rate was 13.2%. The authors stated that while there appears to be substantial literature suggesting the feasibility and safety of minimally invasive surgery for esophageal cancer, the quality of the studies was poor. Flaws included (a) the predominance of case series-low levels of evidence, (b) lack of valid direct comparisons of open versus MIE, (c) heterogeneity of the studies with regard to the type of MIE or hybrid MIE and, thus, lack of generalizability, (d) selection bias-patients selected for minimally invasive surgery are unlikely to have been representative of the general population of esophageal cancer patients (i.e., earlier stage, smaller tumors, and/or less co-morbid), and (e) publication bias-surgeons with unsatisfactory results may have been less inclined to publish their data.

Verhage et al. published a systematic review consisting of 10 case-control studies comparing open to MIE. (42) Blood loss for MIE (compared to open esophagectomy) was uniformly lower in all studies, whereas hospital and ICU length of stay, total complication rate, and pulmonary complications were significantly lower with MIE in most studies. (42) This paper was limited by the heterogeneity of the studies with regards to technique of MIE and both selection and publication bias. A meta-analysis by Nagpal et al., consisting of 12 studies comparing open esophagectomy (n = 612) and MIE or hybrid MIE (n = 672), concluded similar findings as noted by Verhage's group. There were no significant differences in 30-day mortality or anastomotic leak rates. Blood loss, ICU length of stay, overall hospital stay, and total morbidity were significantly lower in the MIE group. (43) A more recent systematic review by Dantoc et al, comparing open to MIE, showed no significant differences in 30-day survival or 5-year survival rates. (44) Furthermore, in a meta-analysis by Sgourakis et al., was found that total complications were lower with MIE and that anastomotic stricture rates were lower with open esophagectomy. (45) Biere et al. published their findings of a meta-analysis; trends were observed in favor of MIE for the following outcomes: major morbidity, pulmonary complications, anastomotic leakage, mortality, length of stay, operating time, and blood loss, but statistical significance was not reached. (46) The limitation of these meta-analyses is that they consisted primarily of nonrandomized and retrospective case-control studies. Ultimately, it was concluded in all three meta-analyses that prospective randomized controlled trials comparing open versus MIE were needed.

Lastly, a large United Kingdom population-based study by Mamidanna et al. analyzed the Hospital Episode Statistics data from April 2005 to March 2010 and included 7,502 esophagectomies, 1,155 (15.4%) of which were MIE. There was no difference between open and MIE groups, respectively, in 30-day mortality (4.3% versus 4.0%) and overall morbidity (38.0% versus 39.2%). (47) Based on these large studies on MIE, total complication rates range from 38% to 46.2% and operative mortality rates range from 1.3% to 4.3% (*Table 2*). The numerous studies comparing open versus MIE (case-control studies and meta-analyses or systematic reviews) suggest that survival is not significantly different, whereas overall morbidity might be similar or possibly improved with MIE. However, the ultimate message is that better data is necessary to claim the benefits of MIE over open esophagectomy. (47)

In 2012, Biere et al published their first randomized controlled trial (RCT), called the TIME trial (Traditional Invasive vs. Minimally invasive Esophagectomy). (3) The TIME trial compares the traditional transthoracic esophageal

Table 2. *Minimal invasive esophagectomy outcomes, institutional series, case-control studies and systematic reviews*

Study	N	Type	Pneymonia %	Leak %	Rln. injury %	Morbitity %	Mortality %
LUKETICH ET AL. (34)	206	MIE	7,7	11,7	3,6	-	1,4
BIZEKIS ET AL. (38)	50	MIE	-	6	-	-	6
RAJAN ET AL. (39)	463	MIE	-	-	-	16	0,9
NGUYEN ET AL. (40)	104	MIE	-	9,6	-	12,5	2,9
BEN-DAVID ET AL. (41)	100	MIE	9	4	7	-	1
GEMMIL ET AL. (36)	1398	MIE	13,2	7,7	-	46,2	2,3
VERHAGEET AL. (42)							
10 CASE-CONTROL		OPEN	22,9	-	-	60,4	3,8
STUDIES		MIE	15,1	-	-	43,8	1,3
NAGBAL ET AL. (43)							
12 CASE-CONTROL	612	OPEN	NO DIFFERENCE				
STUDIES	672	MIE	NO DIFFERENCE				
DANTOC ET AL. (44)							
17 CASE-CONTROL	-	OPEN					4,4
STUDIES	-	MIE					3,0
SGOURAKIS ET AL. (45)		MIE VS					
	1008	OPEN	TOTAL COMPLICATIONS LOWER WITH MIE				
BIERRE ET AL. (46)	1069	MIE VS					
		OPEN	TRENDS FAVORING MIE BUT NOT STATISTICALY SIGNIFICANT				
MAMIDAMA ET AL. (47)	6347	OPEN				39,2	4
	1155	MIE				38	4,3

resection (right thoracotomy and laparotomy) with MIE (right thoracoscopy in prone and laparoscopy) followed by intrathoracic or cervical anastomosis. Patients with resectable intrathoracic and gastro-esophageal junction type I Siewert were randomized for either (I) MIE in prone position or (II) traditional open procedures followed by intrathoracic or cervical anastomosis. Their hypothesis was that patients undergoing MIE will have less morbidity, a shorter duration of the intensive care unit (ICU) admission and a better quality of life than following the traditional approach. They found difference in respiratory infections of 28% between the open group (57%) and the MIE group (29%). The pulmonary infection rate within the first two weeks was 29% (16 patients) in the open group and 9% (5 patients) in the MIE group. The overall in-hospital incidence of pulmonary infections was 34% (19 patients) in the open group and 12% (7 patients) in the MIE group. (3, 48) Explanation for this lower incidence of pulmonary infections found in the MIE group could be explained by several factors, which taken together all might reduce the development of pneumonia. They held the following suppositions. Use of the prone position in comparison with the open thoracotomy in lateral position could be one of the underlying factors for prevention of atelectasis and pneumonia. A second advantage might be the avoidance of a total collapse of the lung during MIE in prone position. Another important underlying factor for the higher rate of pulmonary infection in open procedures could be the thoracotomy wound itself. Not only the development of atelectasis as result of the totally collapsed lung plays a role but also the post-operative discomfort, produced by the wound, causes an increased rate of pulmonary infections. All these factors together could explain the reduced rate of pulmonary infection found in the MIE group in comparison with the open group. In addition, MIE preserved the quality of life better than the open. Hospital stay was significantly shorter in the MIE group (14 versus 11 days). (3,48) The short hospital stay in the MIE group reflects a faster postoperative recovery. Other postoperative data including pathology parameters, major postoperative complications (anastomotic leakage, 7% in the open and 12% in the MIE) and mortality (1.8% versus 3.4%) were not significantly different. Important are the pathology parameters, the total lymph nodes retrieved, resection margins, pathology stage and the numbers of no residual tumor or lymph node metastasis, indicating the safety of the resection was equal between both groups. Interesting was the different rate for vocal cord paralysis, 14% in the open group and only 2% in the MIE. (3, 48) It is evident that pneumatic dissection by CO2 from thoracic cavity into the neck can simplify the dissection in the neck and reduce the recurrent nerve lesions. (48) In conclusion, this randomized trial comparing open esophagectomy for cancer with minimally invasive esophagectomy shows that MIE resulted in a lower incidence of pulmonary infections, a shorter hospital stay, and a better short term quality of life without compromising the quality of the resected specimen.

Undoubtedly MIE is technically complex surgery and therefore issues related to training and learning curves should be addressed before any widespread application. Centers reporting more than 50 cases have lower mortality and morbidity rates than those with lesser experience while apparently performing a more extensive lymph node dissection that could potentially allow higher cure rates. (37) In the Surveillance Epidemiology and End Results (SEER) database, centers performing less than four esophagectomies annually had 5-year survival rates of 17% compared to 34% in centers performing more than 14 esophagectomies per year. (37)

In a publication by H. Osugi and M. Takemura (32), examining the learning curve of video-assisted thoracoscopic esophagectomy, they showed that, the basic skills seem to be acquired during the first 17 cases. The mean risk of pulmonary complications in the first 34 patients was estimated to be the same as that reported after esophagectomy through conventional thoracotomy (25%). Any center contemplating the start of a MIE protocol should consider that their early results are most likely to be worse than the average outcome in the literature, and this must be undertaken when we estimate the initial results that are published from an institute.

Stenosis is unfortunately a common complication after esophagectomy. Orringer reported a dilatation rate of 77% in 1085 patients undergoing transhiatal esophagectomy. (49) The Mayo clinic (50) reported a dilatation rate of 28.6% in their 280 patients undergoing a variety of surgical approaches. In an attempt to minimize the rate of stenosis, a variety of different anastomotic techniques have been tried and reported. When the Mayo Clinic (50) analyzed their results by type of anastomosis, hand-sewn or mechanical side-to-side using a 3.5-mm linear stapler, the rate of stenosis was significantly higher in the hand- sewn group (34.1% vs. 14.7%). Luketich's unit (51) has reported its results in 181 patients who underwent open transhiatal (n = 146) and three-stage (n = 35) esophagectomy. They used a totally mechanical side-to-side isoperistaltic anastomosis (TMA) or hand-sewn (HSM), which included a semimechanical side-to-side technique in 15 patients. Stenosis was defined as symptomatic, unable to pass the endoscope, and requiring more than one dilatation. They found a higher rate of stenosis in the hand-sewn group (45%) compared with the totally mechanical side-to-side isoperistaltic group (18%) ($p = 0.0002$). Furthermore, their leak rate was 11% and was higher in the hand-sewn group (23% vs. 6%). (51)

A team from Canada has also reviewed its series, comparing hand-sewn and mechanical side-to-side isoperistaltic anastomosis in 91 patients over ten years with Siewert I lesions of the cardia who had undergone Ivor-Lewis (n = 49) and transhiatal (n = 42) esophagectomy. (52) The stricture rate was 13.2% and was higher in the hand-sewn group (17% vs. 7.9%), whereas the leak rate was 16.5% and also was higher in the hand-sewn group (22.6% vs. 7.9%), although their differences were not statistically significant. (52) A meta-analysis (53) of randomized controlled trials comparing hand-sewn and stapled anastomoses demonstrated no difference in rate of stenosis or leaks; however, all the stapled anastomoses were circular and all the anastomoses were intrathoracic.

Regarding the technique of esophagogastric anastomosis, Luketich et al. described employing a 25 mm EEA stapler via a small gastrotomy. (9) Campos et al. (54) published their

technique in which a circular stapled anastomosis is performed using a transoral anvil. Their study included 37 patients who underwent minimally invasive ILE using this new stapled technique; anastomotic leak rate was 2.7%, and stricture rate was 13.5%, all of which were treated successfully with endoscopic dilations. Ben David's group (55) have described their technique of completely thoracoscopic side-to-side stapled 6 cm anastomosis during minimally invasive ILE by placing the anvil portion of the stapler through the esophagostomy (which is guided by a large bore nasogastric tube or Bougie dilator) and the cartridge through the gastrotomy. In this small study, there were no postoperative strictures.

Maas et al. (56) performed a review of 12 studies describing various intrathoracic anastomotic techniques during minimally invasive Ivor Lewis Esophagectomy, including descriptions of hand-sewn techniques and mostly stapled techniques. The stapled techniques were either transthoracic or transoral, and the transthoracic stapled techniques varied with regard to (1) left lateral decubitus versus prone positioning; (2) circular versus linear stapled; (3) end-to-side versus side-to-side; (4) use of purse string device, handsewn purse string, endostitch, or linear staple gun and Z-stitch for securing the anvil on the proximal esophageal side. Anastomotic leak rates ranged from 0 to 10%, and anastomotic stricture rates ranged from 0 to 27.5%. (56)

Some surgeons have supported the thoracoscopic mobilization of the esophagus in prone position as a potentially more ergonomic approach with less pulmonary morbidity. Palanivelu et al. published a series of 130 patients who underwent MIE with thoracoscopic esophageal mobilization in prone position using a right prone posterior approach, thus allowing for left lung ventilation with possible intermittent ventilation of the right lung. (33) Mean operative time was 220 minutes (range 160 to 450 minutes). Median ICU stay was one day (range 1 to 32 days). Postoperative pneumonia rate was only 1.54%. (33) They concluded that, the advantages of thoracoscopic mobilization of the esophagus in prone position are mainly shorter anesthesia time; use of single-lumen endotracheal tube to allow intermittent inflation of right lung; decreased lung injury (the lung retraction is avoided), as the lung collapses well because of the positive pressure pneumothorax, aided by gravity in prone position; decreased bronchial and tracheal injuries; excellent exposure of the operative field; and better ergonomics in stance of surgeon. These factors not only shorten total operative time but also decrease traumatic insult to the patient, and this might ultimately lead to better postoperative respiratory functions. (33)

One obvious disadvantage with the prone technique would be if conversion to open is required either electively or urgently. (33,57) Elective conversion due to adhesions would be time-consuming, requiring repositioning of the patient. With both approaches there is potential for significant blood loss. The most likely reason for emergent conversion is bleeding from the azygous vein, aorta, or an aortoesophageal artery. (57) Although a posterior thoracotomy can be performed in this position it is a less familiar surgical approach and can be difficult.

There have been concerns about adequacy of surgical margins, adequacy of lymphadenectomy, and port-site tumor implants in any laparoscopic or thoracoscopic procedure for esophageal cancer. Palanivelu et al, (33) reported they performed two-field lymphadenectomy, routinely including superior and posterior mediastinum and upper abdominal nodes. Mean number of lymph nodes harvested was 18 (range 11 to 32) compared with 10.3 in Nguyen and colleagues (58) series, 6 (range 3 to 12) in Swanstrom and colleagues (59) series, and 19 in Akaishi and colleagues (60) series. Palanivelu et al adhere strictly to all surgical principles to avoid port-site recurrence. They prefer removal of the specimen through a mini-laparotomy rather than through the narrow thoracic inlet as the majority of their patients harbor bulky tumor. They believe that this approach has helped them prevent any recurrences in the neck. With a mean follow-up of 20 months, they have not observed any wound or port-site recurrence. (33)

In 2011 Berger et al (19) published their series and found out that: the R0 resection rates were high in both groups (open and MIE groups), and there were no differences between the groups. All 5 of the R1 resections, that were found, consisted of the circumferential margins being positive and not margins on the esophagus or stomach themselves. Finally, they noted a significant increase in nodal harvest in the MIE group (median 20 versus 9). (19) It is interesting to speculate why lymph node yields are increased in minimally invasive approaches. Berger et al (19) concluded that this is rather multifactorial and is due mainly to improved processing on the part of pathology departments who now appreciate the increased importance of nodal yields, but also with improvements in operative technique. In their thoracoscopic approach, they specifically clear the level 7, 8, and 9 mediastinal nodes. Also, the laparoscopic approach affords a similar 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. (19) In the review of Bierre et al. (46), in the transthoracic esophagectomy group, lymph node retrieval was comparable in total MIE and open MIE categories in the study by Smithers et al. (61) (17 and 16 median respectively), although, Fabian et al. (62) reported significantly more lymph node retrieval in the MIE group compared to the open transhiatal group (15 and 8, respectively). In the transhiatal group, lymph nodes retrieval was comparable in both categories (open versus minimal invasive) in the studies by van den Broek et al. (63) and Scheepers et al. (64) Finally, Decker et al (37) have shown a mean 10-27 lymph nodes were dissected in MIE, depending on the technique adopted, and these numbers are comparable to open surgery and considered adequate.

Related to the trashiatal versus transthoracic esophacectomy debate, is the controversy related to the extent of lymph node dissection. Proponents of extensive lymphadenectomy believe that more accurate pathological staging can be achieved, local control of the disease is better and long-term survival is improved. On the contrary, others claim that extensive nodal dissection only leads to stage migration without improving the overall prognosis, and should complications occur, postoperative

recovery and long-term quality-of-life are adversely affected. (64)

Three-field lymph node dissection (3-FL) was pioneered in Japan that entails lymph node dissection of the upper abdomen, mediastinum and both sides of the neck. (13, 14, 60) Although it was shown a significant proportion of patients will have pre-operatively unsuspected cervical nodes after 3-FL, whether its routine application would lead to better prognosis remains controversial. Such high-risk surgery should only be performed in specialized centers. Current staging system defines regional nodes as extending from the neck through the mediastinum to the celiac axis. However, most would recommend a two-field lymphadenectomy for lower and middle third tumors, while additional cervical lymphadenectomy should be performed for upper third tumors. (65) There is increasing evidence to show that extended lymphadenectomy is related to survival. One international multicenter study (62) showed that the number of lymph nodes resected was an independent prognostic factor in addition to age, gender, cell type, presence of nodal metastases, number of nodes involved, and depth of tumor invasion. A recent international multicenter study showed that in order to maximize survival, the optimal number of lymph node that should be dissected is related to the T stage: 10 nodes should be resected for T1 lesions, 20 for T2, and 30 or more for T3/T4 disease. (66) These correlated with the data and recommendations of the seventh edition of the AJCC cancer staging manual and it underlined the need of an adequate lymphadenectomy of 12-22 resected nodes. (67) Of course, in practice it is impossible to count the number of nodes removed at the time of surgery, this is merely used in retrospect to assess the quality and adequacy of lymphadenectomy. One should aim at resecting as many regional nodes as possible to provide therapeutic benefit in terms of locoregional disease control and long-term survival, balancing the extent of lymphadenectomy with morbidity. (65,67)

The optimal lymphadenectomy for squamous cell carcinoma of the lower thoracic esophagus is still debatable. Three-field lymphadenectomy can, most likely, achieve a R0 resection and accurate staging. The question is whether it definitely improves the long-term survival of patients. However, most data are available from nonrandomized retrospective historical studies in Japan. Igaki et al. (68) reported that the three-field lymphadenectomy could prolong the survival time of patients with squamous cell carcinoma of the lower thoracic esophagus compared to 2-field lymphadenectomy for nodal metastases present in the upper and/or middle mediastinum. Fujita et al. (69) reported that there is no difference in survival rate for patients with lower thoracic esophageal cancer between the two procedures of lymphadenectomy. Three-field lymphadenectomy has its obvious advantages and disadvantages. (70) Hence, two-field lymphadenectomy seems to be a more reasonable choice of treatment for squamous cell carcinoma of the lower thoracic esophagus. This viewpoint is far outweighed by the fact that the emphasis on three-field lymphadenectomy has shifted to lymphadenectomy along the recurrent laryngeal nerve chains, where lymph nodes could be dissected through a two-field lymphadenectomy. (70)

Conclusion

Minimally invasive surgery has the advantages of better cosmetic results, reduced operative stress, postoperative immobility, and pain. These advantages are obtained by minimizing the incisions to obtain access to natural cavities, and by that, decreasing the external surgical stress. Minimally invasive surgery does not change, however, the internal part of the operation and the surgical stress determined by it. The minimally invasive approach has gained rapid acceptance and has become the gold-standard operation in which external stress is higher than internal stress, such as for cholecystectomy and hiatal hernia repair. (71) In operations in which internal surgical stress is intensive, such as a Whipple procedure, the minimally invasive approach is questionable. (72) This is also true for Minimally Invasive Esophagectomy (MIE). (15,71) Even with a minimally invasive approach, the clinical consequences of intense internal aggression, such as systemic inflammatory response syndrome, are still noticed after MIE. (73) However, there are strong literature data to suggest that MIE comparing to open esophagectomy procedures have less morbidity with less overall in-hospital incidence of pulmonary infections and shorter duration of ICU admission. In addition, MIE preserve the quality of life better than the open procedures, with faster post-operative recovery. Postoperative data including pathology parameters, major post-operative complications, such as anastomotic leakage and mortality, are not significantly different between MIE and open techniques, indicating the safety of the resection after the minimally invasive procedure. Of course, it is a technically complex surgery with a learning curve of more than 50 cases needed to obtain low rates of mortality and morbidity.

Several minimally invasive approaches for esophagectomy have been described: total transhiatal laparoscopic approach, esophagectomy using right thoracoscopy, combined laparoscopic and right thoracoscopic esophagectomy, esophageal resection through mediastinoscopy, robot-assisted esophagectomy and hybrid techniques. Transhiatal surgery seems best suited to early stage disease including multifocal high-grade dysplasia in patients with very long Barrett's segments, especially, for adenocarcinoma of the esophagogastic juction and lower third of esophagus. The thoracoscopic approach can be done either with the minimally invasive Ivor Lewis esophagectomy, or with the minimally invasive three-stage operation. Most surgeons use these techniques for carcinomas of the middle and upper third of the esophagus. The video-assisted mediastinoscopic transhiatal esophagectomy avoids thoracotomy and reduces bleeding compared with traditional transhiatal esophagectomy, and the resected mediastinal lymph nodes are more. The robot-assisted methods have encouraging results, but the time required is too long and the published data little for more widely acceptance. Finally, hybrid techniques have been established planning to reduce the operating time, making more familiar to surgeons the new minimal invasive approaches and without compromising oncological outcomes.

Closing, MIE has been investigated mainly in case-control studies and bias may have been introduced simply by the study

design. More randomized trials comparing MIE with open esophagectomy are necessary in order to evaluate outcomes more efficiently.

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