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IMPLEMENTATION OF A TOTALLY MINIMALLY INVASIVE ESOPHAGECTOMY PROGRAM FOR CANCER IN A HIGH-VOLUME CENTER:

COMPARISON OF INITIAL SERIES RESULTS WITH TRADITIONAL OPEN TECHNIQUE

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ABSTRACT

Introduction

The minimally invasive approach is becoming increasingly popular; in fact, it has demonstrated non-inferior surgical and oncologic outcomes compared with open esophagectomy, with better short-term outcomes. Advantages include shorter hospital and ICU stays, fewer pulmonary infections, and less intraoperative blood loss. However, minimally invasive esophagectomy requires highly developed minimally invasive surgical skills and is a technically difficult procedure. Even in a tertiary center, developing a minimally invasive program takes time and has a protracted learning curve before a plateau of ideal results is reached.

Aim

The purpose of this study is to evaluate the safety and efficacy of implementing a totally minimally invasive esophagectomy program for cancer in a high-volume center. In addition, it aimed to evaluate the impact of the learning curve on perioperative and oncologic outcomes. Survival and disease-free survival were included as secondary endpoints.

Materials and methods

This study is a prospective non-randomized control study from a single center. From the start of the minimally invasive program in June 2018 to October 2022, data were gathered on all consecutive patients who underwent elective Ivor Lewis esophagectomy at the Upper G.I. Surgery Unit “General surgery I” of Padova University. Patients undergoing Minimally Invasive Ivor Lewis Esophagectomy were assigned to the MIE group (“minimally invasive esophagectomy”), those undergoing Open Ivor Lewis Esophagectomy to the OE group (“open esophagectomy”). By comparing the perioperative and oncological outcomes of patients who underwent MIE to those of patients treated with OE during the same period, we evaluated the safety and efficacy of the minimally invasive approach in the treatment of esophageal cancer. Subsequently, the MIE group was divided into two groups: Early Experience (“EE”) and Late Experience (“LE”) group. By comparing the perioperative and oncological outcomes between the two groups we evaluated the presence and the impact of a learning curve.

Results

During the inclusion period, 61 patients underwent MIE and 138 underwent OE. The mean operative time was shorter for the open approach than for the minimally invasive approach (295 ± 62,2 vs. 363 ± 56,1 minutes, P value < 0,001). The average number of lymph nodes harvested was higher during MIE than during OE (27,4 ± 10,1 vs 20,8 ± 9,6 lymph nodes, P value < 0,001). The number of total blood transfusions was lower in the OE compared to the MIE group (0,1 ± 0,3 vs 0,7 ± 1,7 blood units, P value 0,019). No differences were found regarding surgical radicality or postoperative complications type and severity. Hospital stay, ICU stay and 90-days mortality and readmission rates were similar between the two groups. Comparing the patients undergone MIE in the early experience period (31 patients) to the ones of the late experience period (30 patients) we observed a decrease in the mean number of metastatic lymph nodes extracted (2,7 ± 4,0 vs. 0,3 ± 0,6 lymph nodes, P value 0,002), in the infective and thromboembolic complications rates (respectively 54,8% vs 13,3%, P value < 0,001, and 16,1% vs 0%, P value 0,022), and in the average ICU total stay (1,6 ± 2,4 vs 0,6 ± 1,5 days, P value < 0,049).

Conclusions

The findings of this study support the safety and efficacy of implementing a totally minimally invasive esophagectomy program for cancer in a high-volume center. In comparison to open technique, surgical and oncological outcomes, postoperative complication rates, morbidity and mortality rates were not compromised by the learning curve effect and met current international standards. According to our observations, MIE results in higher rates of lymph node yield, both in the abdominal and thoracic fields. We therefore propose that the effect of laparoscopic magnification can aid in a more accurate and precise lymph node dissection. Comparing the outcomes of the early experience with those of the late experience, we discovered improving trends in postoperative complication and recovery rates. In our high-volume center's experience, improving these outcomes has required 25 to 30 cases.

1. INTRODUCTION

1.1. Esophageal cancer

1.1.1. Epidemiology

According to the Global cancer statistics 2020 esophageal cancer has a seventh-place incidence (604,000 new cases) and sixth-place overall mortality (544,000 deaths). There is a 2- to 3-fold difference in incidence and mortality rates between the sexes, with men accounting for roughly 70% of cases. Due in part to China's heavy burden, Eastern Asia has the highest regional incidence rates for both men and women, followed by Southern Africa, Eastern Africa, Northern Europe, and South Central Asia (Fig. 1).[1]

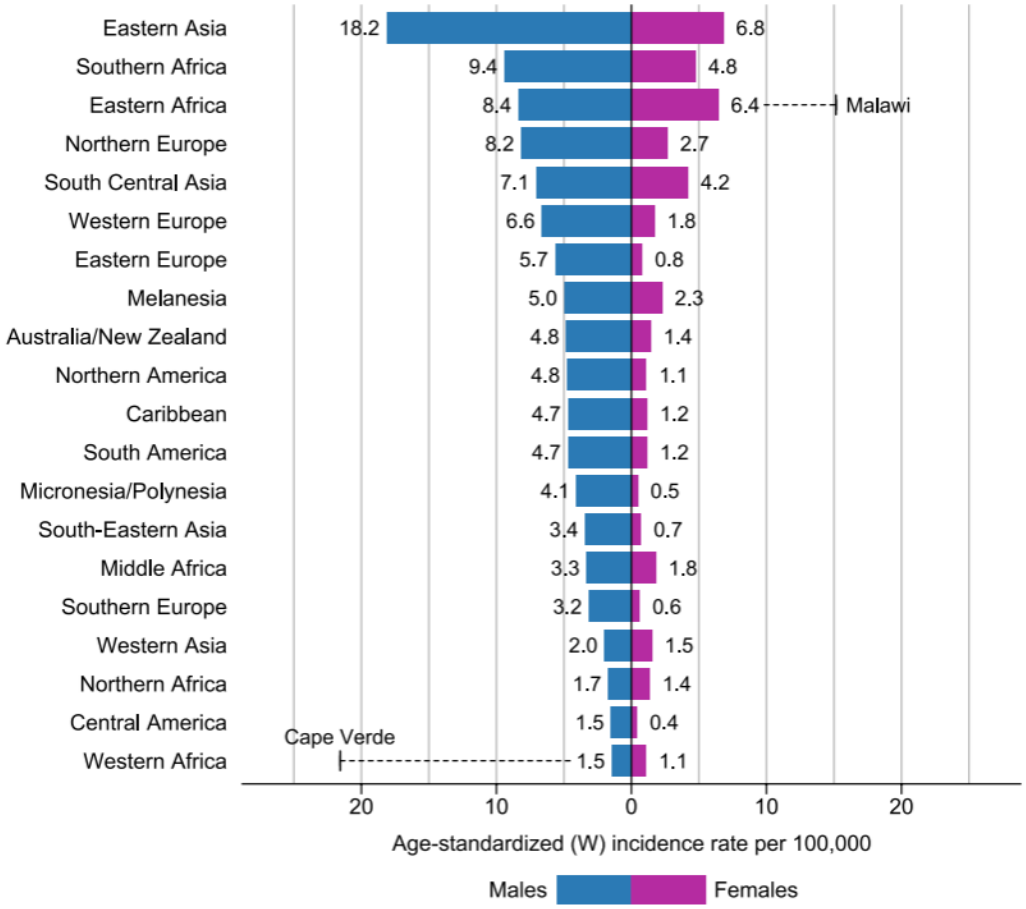


Figure 1. Esophageal Cancer Age-Standardized Rates by Sex in 2020.[1]

The highest national rates for men and women are overlaid, and rates are presented in descending order of the age-standardized rate for men around the world (W).

1.1.2. Risk factors

The geographic variation in the incidence of esophageal cancer significantly differs between the 2 most common histologic subtypes: Squamous cell carcinoma (SCC) and Adenocarcinoma (AC), which also have quite distinct etiologies.[2]

The incidence rates of SCC are highest in populations in South-Eastern and Central Asia, Eastern Africa, and South America, accounting for about 87% of all esophageal cancers worldwide. Only 11% of all esophageal cancers are EAC, with Northern and Western Europe, Oceania, and Northern America having the highest burdens (Fig. 2).[3]

Smoking and heavy drinking and their combined effect are the major risk factors for SCC in western settings. The incidence of esophageal SCC in some high-risk areas in Asia (e.g. China) is generally declining: this trend could be explained by economic gains and dietary improvements; in contrast, in several high-income countries (e.g. USA, UK, Australia, France) the decline in cigarette smoking is believed to be the main cause of the decreased incidence rate.

AC represents approximately two-thirds of esophageal cancer cases in high-income countries, with Barrett's esophagus, excessive body weight, and GERD among the key risk factors.[2] Due to an increase in both GERD and excessive body weight, incidence rates of AC are rapidly increasing across high-income countries. In many high-income countries, AC is expected to surpass SCC and being overweight is anticipated to play an increasingly significant role in the burden of esophageal cancer in the future.[4]

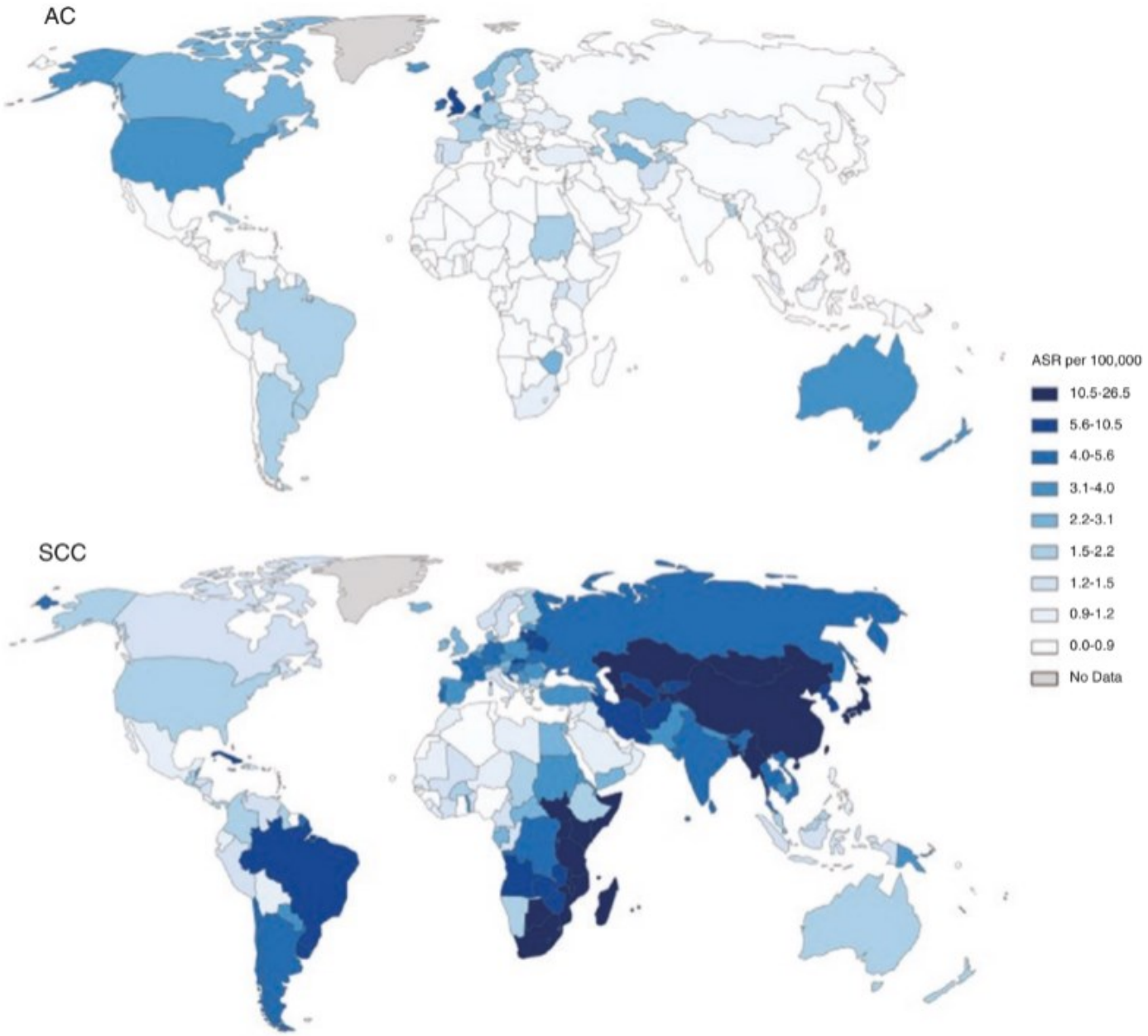


Figure 2. Age standardized incidence rate per 100,000 population of esophageal SCC and AC in men.[3]

1.1.3. Anatomy

The four layers of the esophageal wall are mucosa, submucosa, muscularis propria and adventitia. The mucosal layer is made of squamous epithelium, lamina propria and muscularis mucosa. The submucosa, the strongest layer of the esophagus wall, is composed of elastic and fibrous tissue. There are two layers to the esophageal muscle: an inner circular layer and an outer longitudinal layer. Skeletal muscle makes up the top third and smooth muscle the lower two thirds of the esophageal musculature. The adventitia is made up of connective tissue that fuses with the connective tissue around it. The esophagus lacks a serosal layer, unlike the rest of the gastrointestinal system.[5]

The esophagus can be anatomically divided into three parts: the cervical, thoracic, and abdominal esophagus. It is located between the hypopharynx and the stomach. The zone of the esophagogastric junction is divided into the esophageal side and gastric side and is defined as the region between 2 cm in esophagus and 2 cm in the stomach from the esophagogastric junction. The abdominal esophagus is included in this zone (fig. 3).[6]

Small branches from nearby organs share the esophageal vascularization. The inferior thyroid arteries, bronchial arteries, inferior phrenic arteries, left stomach artery, unidentified vessels branching straight from the thoracic aorta, and other blood vessels feed the arterial blood supply. The left stomach, hemiazygos, and inferior thyroid veins all receive blood drainage. Lymph from the cervical and upper-mid thoracic esophagus mostly drains into the cervical, paratracheal, and subcarinal lymph nodes, whereas the lower thoracic and abdominal esophagus preferentially drains into the diaphragmatic, paracardial, left gastric, and celiac nodes.[7]

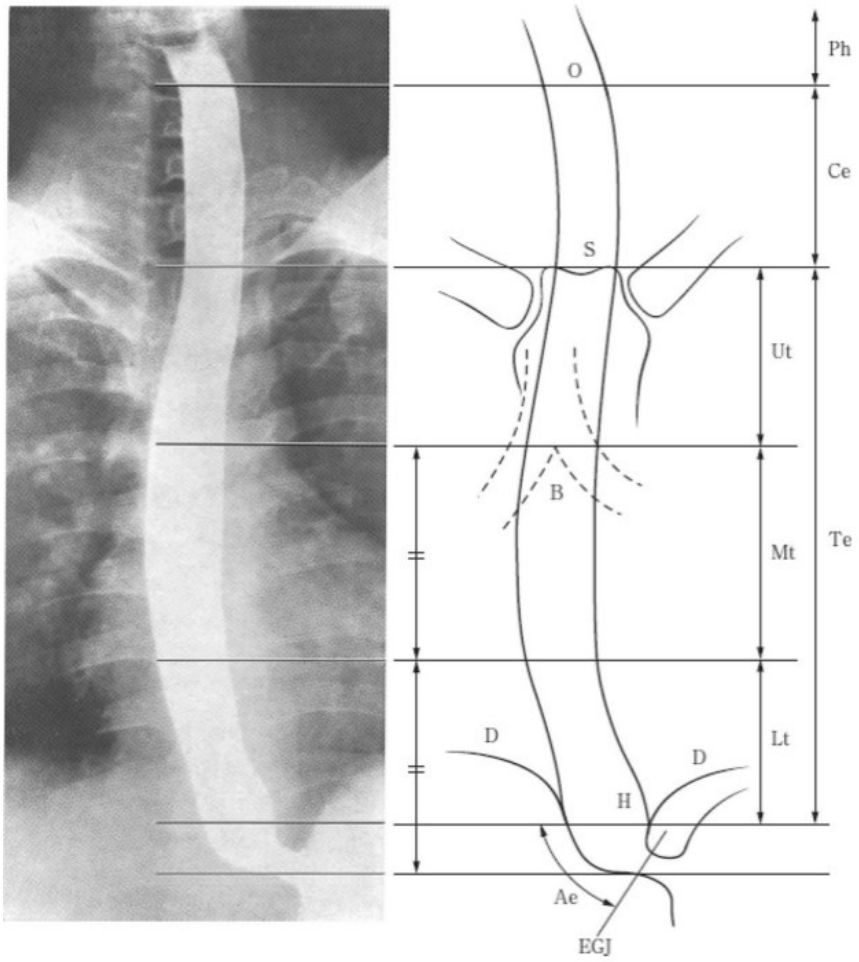


Figure 3. esophageal segments.[6]

Cervical esophagus (Ce): extends from the esophageal orifice to the sternal notch.

Thoracic esophagus (Te): From the sternal notch to the superior margin of the esophageal hiatus.

Upper thoracic esophagus (Ut): From the sternal notch to the tracheal bifurcation.

Middle thoracic esophagus (Mt): The proximal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction.

Lower thoracic esophagus (Lt): The thoracic part of the distal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction.

Abdominal esophagus (Ae): The abdominal part of the distal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction (from the superior margin of the esophageal hiatus to the esophagogastric junction).

1.1.4. Clinical presentation and Diagnosis

The most common symptom at diagnosis is dysphagia, which typically develops when the tumor occupies 1/3 of the lumen. Weight loss is also a typical symptom that is usually associated with asthenia and anorexia. The presence of epigastric or retrosternal pain radiating to the back may indicate the mediastinal diffusion of the disease. Hiccup can develop due to infiltration of the phrenic nerve and diaphragm whereas voice hoarseness and cough could emerge due to the involvement of superior laryngeal nerves. Regurgitation and sialorrhea can also be present as well as hematemesis and melena.

Patients with symptoms that could be esophageal cancer must undergo specific tests, not only for the diagnosis but also for the staging of the disease, especially when there are several risk factors.[8]

Esophagogastroduodenoscopy (EGDS) is performed with the goal of determining the presence and location of esophageal neoplasia and to biopsy any suspicious lesions. To help with treatment planning, it is important to take careful note of the tumor's position in relation to the teeth and EGJ, its length, the degree of circumferential involvement and obstruction. If Barrett esophagus is present, its position, circumference, and length should be assessed using the Prague criteria, and any mucosal nodules should be meticulously recorded. To provide enough material for histologic interpretation, six to eight biopsies should be performed using standard-size endoscopy forceps. The pathology report should include the presence or absence of invasion, histologic type, Grade and Presence or absence of Barrett esophagus.[9]

1.2. Classification and staging

1.2.1. Siewert classification

Siewert tumor type should be assessed in all the patients with adenocarcinoma involving the esophagogastric junction[9]. They are differentiated into the following three distinct tumor entities (fig. 4).

Siewert Type I: adenocarcinoma of the lower esophagus with the epicenter located within 1 cm to 5 cm above the anatomic EGJ.

Siewert Type II: true carcinoma of the cardia with the tumor epicenter within 1 cm above and 2 cm below the EGJ.

Siewert Type III: subcardial carcinoma with the tumor epicenter between 2 cm and 5 cm below the EGJ, which infiltrates the EGJ and lower esophagus from below.[13]

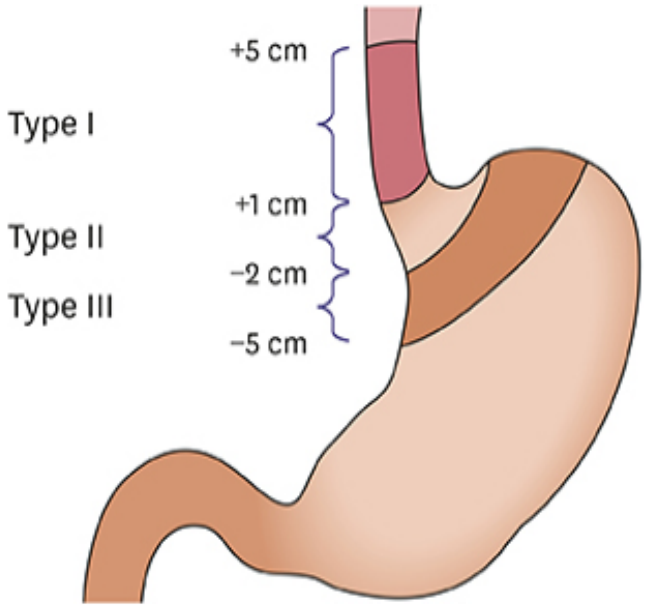


Figure 4. Siewert classification of Adenocarcinoma of the esophagogastric junction.[14]

1.2.2. TNM staging

Clinical staging should be carried out to determine resectability prior to surgery using chest and abdomen computed tomography scan (CT scan), whole-body Fluorodeoxyglucose positron emission tomography (FDG-PET) and endoscopic ultrasound (EUS). The integrated PET/CT scan is preferable.[9]

Chest and abdomen CT scan with contrast media is used to accurately define the primary tumor stages, the involvement of adjacent structures and the presence of distant metastasis, generally located in the liver and lungs. In terms of detecting distant metastasis, PET/CT is superior to CT in the staging of esophageal cancer, with a higher sensitivity (71% vs. 52%, respectively) and a similar specificity (93% vs. 91%).[10]

Endoscopic ultrasonography (EUS) assesses the loco-regional stage of esophageal cancer; the T and N stages are calculated through the assessment of the tumor invasion depth and the local lymph node metastases. The operator dependence and the echoendoscope's inability to pass through stenotic lesions are the two biggest drawbacks. The best diagnostic tool for determining the loco-regional involvement, however, is EUS, which has been shown to be superior to CT scanning in T and N staging.[11]

It has been demonstrated that minimally invasive surgical staging, which uses laparoscopy and, on occasion, thoracoscopy, is more accurate than traditional imaging methods. Improved evaluation of locoregional disease and improved detection of occult distant metastases are two key benefits of minimally invasive surgical staging over non-invasive staging techniques.[12]

The TNM staging system developed by the American Joint Committee on Cancer is used to describe esophageal cancer staging. Using this method, the extent of tumor invasion (T), the number of local lymph nodes affected (N), and any distant metastases (M) can all be described. Also the grade of histologic differentiation (G) can be characterized and subdivided into G1, G2 and G3, that is well-, moderately- and poorly-differentiated.[15,16]

If the tumor has spread to the adventitia layer or has affected the pleura, peritoneum, pericardium, or diaphragm, it is thought to be resectable (T1-T4a). If it invades the aorta, trachea, left major bronchus, azygos vein, or vertebral body, it is regarded as

being non-resectable (T4b) (Fig. 5).[15]

Regional lymph nodes are found in the periesophageal tissue, from the upper esophageal sphincter to the celiac trunk; other lymph nodes involvement is considered as metastasis (Fig. 6).[17]

Clinical staging, based on imaging and biopsy, is a useful tool for determining cancer treatment, although it could not accurately reflect the pathology stage or the prognosis.[16] The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) have developed the standard staging approach for esophageal cancer, which offers distinct classifications for clinical, post-neoadjuvant and pathologic stages (Tab. I, Tab. II, Tab. III). The anatomic and pathologic characteristics of the resected specimen from an esophagectomy are used to determine the pathologic stage.[17]

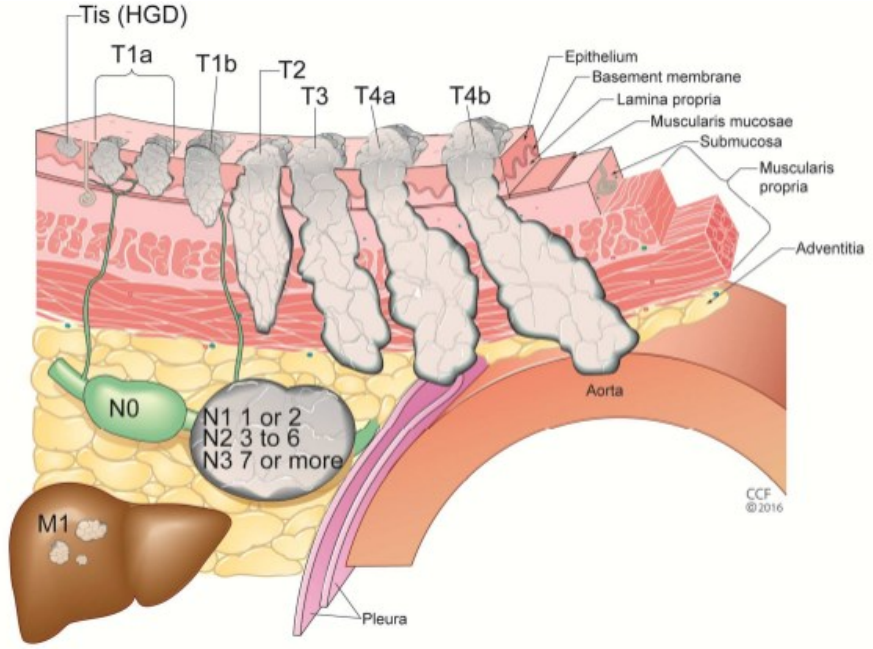


Figure 5. TNM categories.[18]

Tis: high-grade dysplasia;

T1: invasion of lamina propria, muscularis mucosae, or submucosa;

T1a: cancer invades lamina propria or muscularis mucosae;

T1b: cancer invades submucosa;

T2: invasion of muscularis propria;

T3: invasion of adventitia;

T4: invasion of local structures;

T4a: invasion of adjacent structures such as pericardium, pleura, peritoneum, azygos vein, or diaphragm;

T4b: cancer invades major adjacent structures, such as trachea, aorta, or vertebral body.

N0: no regional lymph node metastasis;

N1: 1 to 2 regional lymph nodes involved by metastasis;

N2: 3 to 6 regional lymph nodes involved by metastasis;

N3: 7 or more regional lymph nodes involved by metastasis.

M0: no distant metastasis;

M1: distant metastasis.

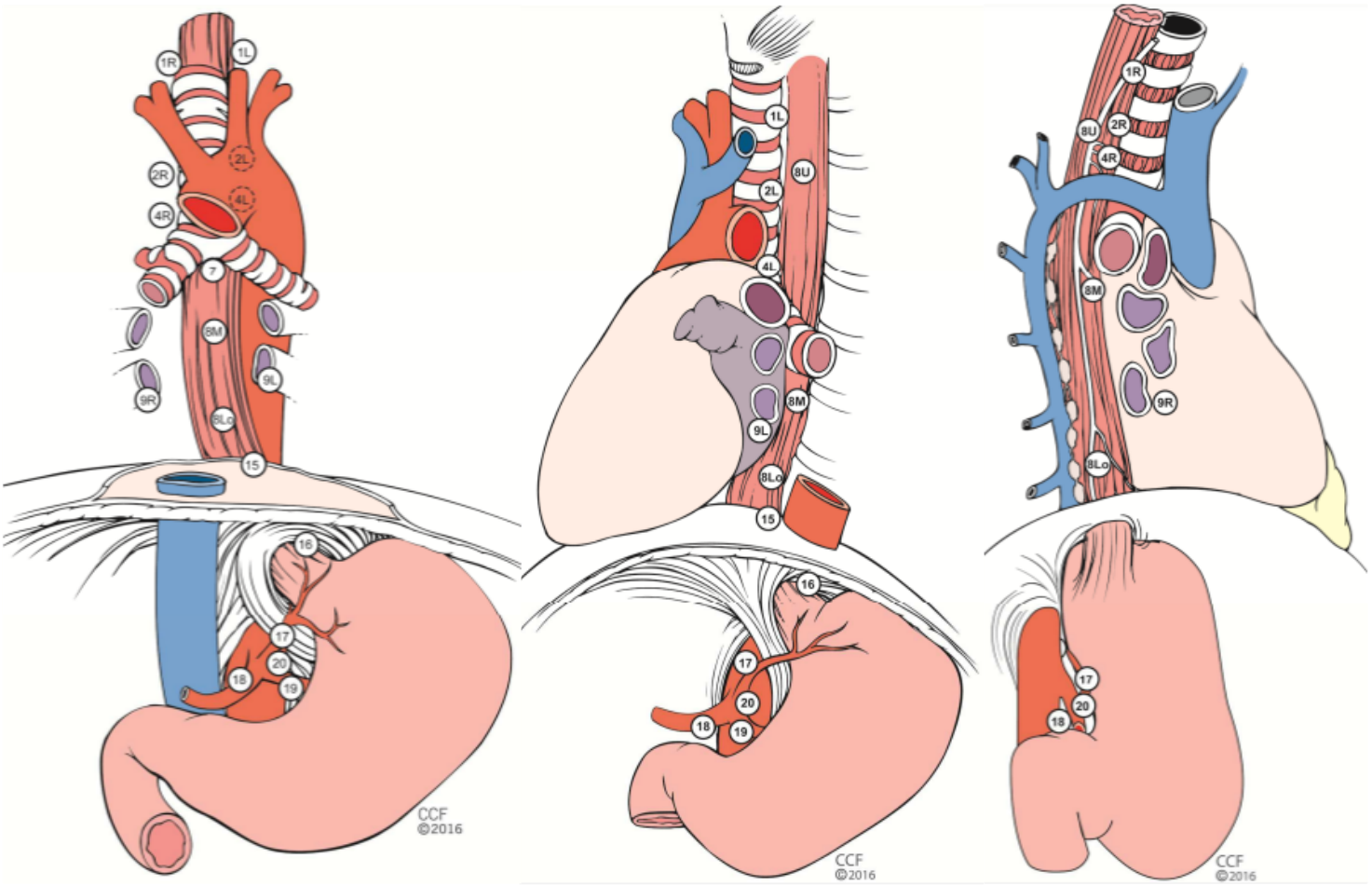


Figure 6. Lymph node maps for esophageal cancer.[17]

The images show (left-right): anterior aspect, left aspect and right aspect.

1R: right lower cervical paratracheal nodes

1L: left lower cervical paratracheal nodes

2R: right upper paratracheal nodes

2L: left upper paratracheal nodes

4R: right lower paratracheal nodes

4L: left lower paratracheal nodes

8U: upper thoracic paraesophageal nodes

8M: middle thoracic paraesophageal nodes

8Lo: lower thoracic paraesophageal nodes

15: diaphragmatic nodes

7: subcarinal nodes

9R: right pulmonary ligament nodes

9L: left pulmonary ligament nodes

16: paracardial nodes

17: left gastric nodes

18: common hepatic nodes

19: splenic nodes

20: celiac nodes

Table IA. Clinical stages of Squamous Cell Carcinoma[17]

	N0	N1	N2	N3	M1
Tis	0				
T1	I	I	III	IVA	IVB
T2	II	II	III	IVA	IVB
T3	II	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

Table IB. Clinical stages of Adenocarcinoma[17]

	N0	N1	N2	N3	M1
Tis	0				
T1	I	IIA	IVA	IVA	IVB
T2	IIB	III	IVA	IVA	IVB
T3	III	III	IVA	IVA	IVB
T4a	III	III	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

Table IIA. Pathological stages of Squamous Cell Carcinoma[17]

			N0					
			L	U/M	N1	N2	N3	M1
Tis		0						
T1a	G1	IA	IA		IIB	IIIA	IVA	IVB
	G2-3	IB	IB					
T1b		IB			IIB	IIIA	IVA	IVB
T2	G1	IB	IB		IIIA	IIIB	IVA	IVB
	G2-3	IIA	IIA					
T3	G1	IIA	IIA		IIIB	IIIB	IVA	IVB
	G2-3	IIA	IIB					
T4a		IIIB			IIIB	IVA	IVA	IVB
T4b		IVA			IVA	IVA	IVA	IVB

Table IIB. Pathological stages of Adenocarcinoma[17]

			N0	N1	N2	N3	M1
Tis		0					
T1a	G1	IA	IA	IIB	IIIA	IVA	IVB
	G2	IB	IB				
	G3	IC	IC				
T1b	G1	IB	IB	IIB	IIIA	IVA	IVB
	G2	IC	IC				
	G3						
T2	G1	IC	IC	IIIA	IIIB	IVA	IVB
	G2	IIA	IIA				
	G3						
T3		IIB	IIB	IIIB	IIIB	IVA	IVB
T4a		IIIB	IIIB	IIIB	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVA	IVB

Table III. neoadjuvant stages: The groups are identical for both histopathologic cell types[17]

	N0	N1	N2	N3	M1
T0	I	IIIA	IIIB	IVA	IVB
Tis	I	IIIA	IIIB	IVA	IVB
T1	I	IIIA	IIIB	IVA	IVB
T2	I	IIIA	IIIB	IVA	IVB
T3	II	IIIB	IIIB	IVA	IVB
T4a	IIIB	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

1.3. Treatment

1.3.1. Endoscopic resection for superficial esophageal cancer

Lymph node metastases of SCC increase gradually as tumor depth increases. According to the depth of invasion, T1a tumors are divided into three categories: m1 cancers invade the epithelium, m2 lesions invade the lamina propria, and m3 tumors reach the muscularis mucosa. Several studies show no sign of lymph node metastases until the m3 level.[19,20] Most recent NCCN guidelines suggest endoscopic resection (ER) as the preferred approach in pTis and pT1a tumors in fit patients and that can be associated with ablation.[9] T1a SCC tumors treated with ER have a documented high rate of survival, with a 5-year overall survival rate of over 95%.[19]

In AC, the likelihood of lymph node metastasis in T1a cancer is thought to be between 1.3 and 5%.[21,22] This risk rises to as much as 27% for T1b adenocarcinoma, in contrast.[23] The primary indicator of lymph node metastasis has been identified as lymphovascular invasion.[24] Lymph node metastasis and submucosal invasion have also been found to be related to tumor size greater than 2 cm and poor differentiation.[22] Sm1, Sm2, and Sm3 are additional categories for T1b AC. According to estimates, the rate of positive lymph nodes in AC limited to sm1 is 0%, while it is 42.9% in sm2/3. Consequently, sm1-limited AC or tumors confined to the upper third of the submucosa (superficial pT1b) are also candidates for local treatment, as are pTis and pT1a tumors.[25] Furthermore, it has been established that the risk of positive nodes for sm1-limited tumors is less than the risk of esophagectomy surgery.[26] 93.8% of patients who underwent endomucosal resection (EMR) for mucosal adenocarcinoma achieved long-term complete remission, with a 5-year survival rate of 91.5%, according to a study that monitored 1000 patients with the disease over a mean period of 56 months.[27]

1.3.2. Neoadjuvant treatment

Perioperative chemotherapy was chosen as the main strategy in Europe and the United States as a result of data from the phase III MAGIC study in the United Kingdom.[28] NCCN guidelines suggest neoadjuvant treatment for locally advanced tumors, defined as clinical lymph node involvement or clinical T3-T4a, regardless of lymph node status, in the absence of distant metastases.[9] Preoperative treatment for esophageal/GEJ cancer patients reduced all-cause mortality by 13% in patient with AC when compared to surgery alone, according to a meta-analysis of 10 randomized trials. It also revealed a non-significant trend toward lower all-cause death rates when preoperative chemotherapy was replaced with preoperative chemoradiation.[29] On the other hand, radiotherapy alone followed by surgery was demonstrated not superior to surgery alone in terms of survival.[30] According to the literature, preoperative chemoradiotherapy combined with surgery produces the best results when treating locally advanced esophageal cancer; however, to more precisely define the function of preoperative therapy, preoperative chemoradiotherapy must be compared with chemotherapy alone. Due to divergent beliefs and medical practices throughout the world and the absence of a trial that directly compares these two well-established treatment methods, the standard of care is still up for dispute.[30]

A restaging is carried out following the neoadjuvant therapy to see if the tumor responded. This usually necessitates repeating a CT scan, an 18-FDG PET-CT scan, and an endoscopy with biopsy. The possible outcomes, according to the RECIST guidelines[31] are the following:

- complete response (CR), defined as disappearance of all target lesions. Any pathological lymph nodes must have a reduction in the short axis to <10 mm.
- Partial response (PR), where there should be at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Stable disease (SD), where neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD takes place, taking as reference the smallest sum diameters while on study.
- Progression of disease (PD), for which must increase by at least a 20% the sum of diameters of target lesions, taking as reference the smallest sum in study.

In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

1.3.3. Surgery

Esophagectomies are complex procedures with mortality < 5%[32] and reasonable morbidity (24%)[33] when carried out in high-volume centers. According to the Esophageal Complications Consensus Group (ECCG), pneumonia (14.6%), atrial dysrhythmias (14.5%), esophageal-enteric leak (11.4%), chyle leak (4.7%), and recurrent laryngeal nerve damage (4.2%) are the most common complications following esophagectomy. Mortality is 2.4% at 30 days and 4.5% at 90 days.[34]

For deeply infiltrating (sm2, sm3) T1b N0 and T2 N0 disease, with lesions < 3 cm and well-differentiated, first-line surgery is the preferred treatment, but higher stages of tumors are best treated with neoadjuvant therapy before surgery, as discussed in the previous chapter.[9]

The goal of surgery is a radical resection since resections that have positive margins are characterized by poor prognoses and significantly lower survival rates.[35] There is currently no international agreement on the minimum proximal resection margin (PM) length required to reduce the risks of non-radical resection, and there is no conclusive proof that the length of the PM affects survival. A PM > 2 cm may be sufficient, given the data available and the shrinking phenomenon.[36] An essential component of treating esophageal cancer is the extent of the lymphadenectomy; a proper lymphadenectomy has been linked to significantly longer overall survival. The NCCN guidelines recommend removing at least 15 lymph nodes for proper staging, however the number of indicated lymph nodes is still up for debate.[9,37] There are several ways to do surgical resection. The decision is taken based on the cancer's stage and location, the patient's health, the morbidity and death rates connected to each strategy, as well as the preferences and abilities of the surgeon.[34] The NCCN recommendations do not specify a preferred surgical approach but do state that the gastric conduit is the recommended conduit option if the stomach is pathology-free and long enough.[9] The surgical techniques will be explored in more detail in chapter 1.4.

1.3.4. Postoperative management

Based primarily on the Intergroup 116 study, post-operative chemoradiation is the standard-of-care in the United States for GEJ/gastric cancers after upfront resection.[38] Postoperative therapy is recommended by the NCCN guidelines in all the cases of AC in which the surgical resection margins are microscopically (R1) or macroscopically (R2) involved by the tumor. The adjuvant treatment of SCC in which the surgical resection margins are positive is similar to the one of AC in patients that did not receive neoadjuvant treatment, while in patients that receive pre-operative treatment surveillance and palliative treatment are preferred. In case of negative surgical resection margins (R0), the postoperative management differs depending on the histologic tumor type, the preoperative treatment received and the N and T parameters (Fig. 7, Fig. 8). Fluoropyrimidine-containing regimens are typically the way to go, and if it is not started prior to surgery, radiation therapy is usually associated.[9]

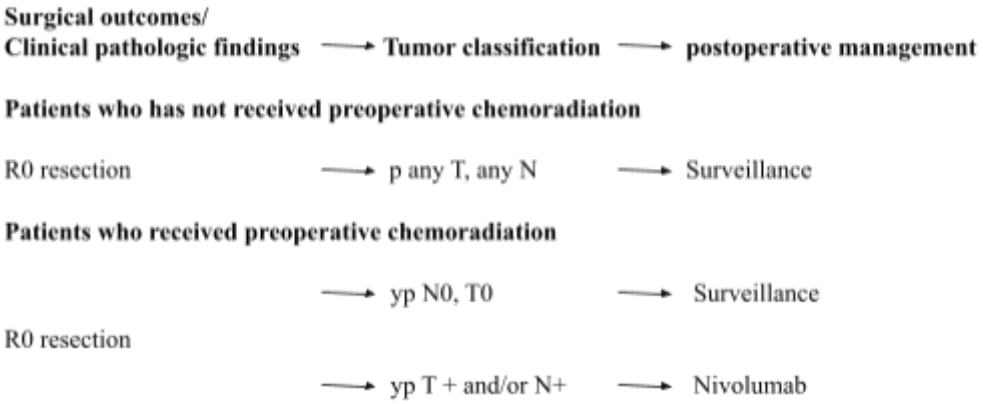


Figure 7. Postoperative management of patient with SCC and negative surgical resection margins.[9]

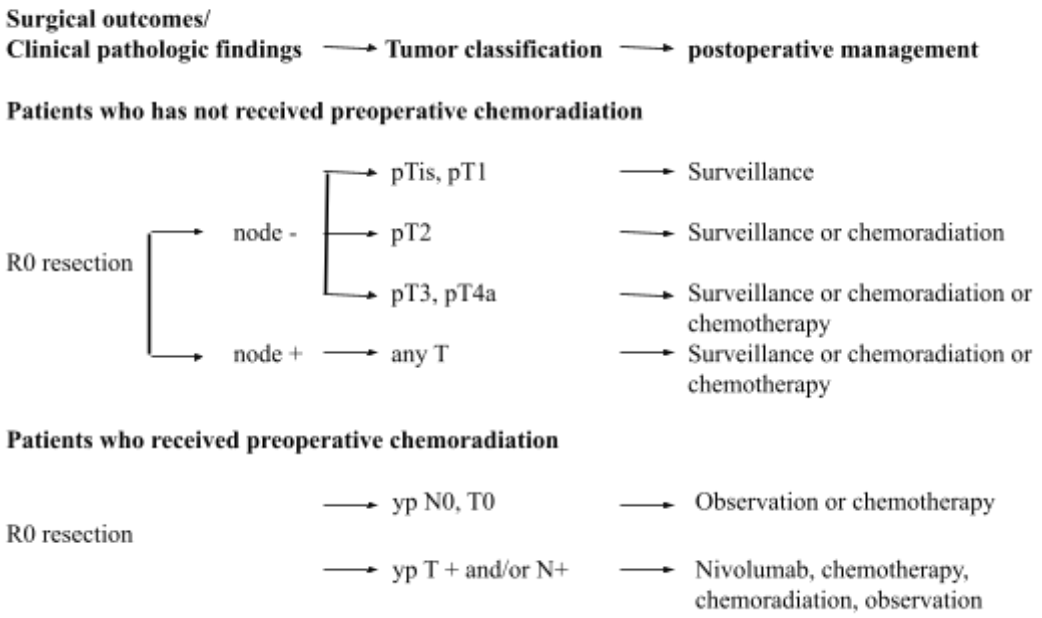


Figure 8. Postoperative management of patient with AC and negative surgical resection margins.[9]

1.3.5. Non-surgical candidates

Definitive chemoradiotherapy is preferred for non-surgically fit patients, even though they present a resectable disease, and for those who refuse surgery. Palliative radiotherapy or Best supportive care/Palliation are the preferred methods if the patients cannot tolerate chemotherapy. Systemic therapy can be tried for unresectable locally advanced, locally recurrent, or metastatic disease in patients with a Karnofsky performance score ≥ 60% or an ECOG performance score ≤ 2. Best supportive care/Palliation are the preferred strategies if the performance status is worse.[9]

1.3.6. Follow-up

Survival after esophagectomy depends on the pathologic stage group (Fig. 9).[15]
90% of relapses happen within the first two years following the end of local therapy. With no high-level evidence to guide the development of algorithms that balance benefits, risks and costs; surveillance strategies after successful therapy for esophageal and EGJ cancers remain debatable.[9] According to the NCCN recommendations, patients should be evaluated on an ongoing basis with a thorough history collection and physical examination every 3-6 months for 1-2 years, every 6-12 months for 3-5 years, and then annually. Additionally necessary are nutritional counseling and assessment. Based on the clinic, it is also necessary to consider the prescription of the chemistry profile, complete blood count, imaging studies, upper GI endoscopies and biopsies. Anastomotic stenosis should be treated with endoscopic dilatation.[9]

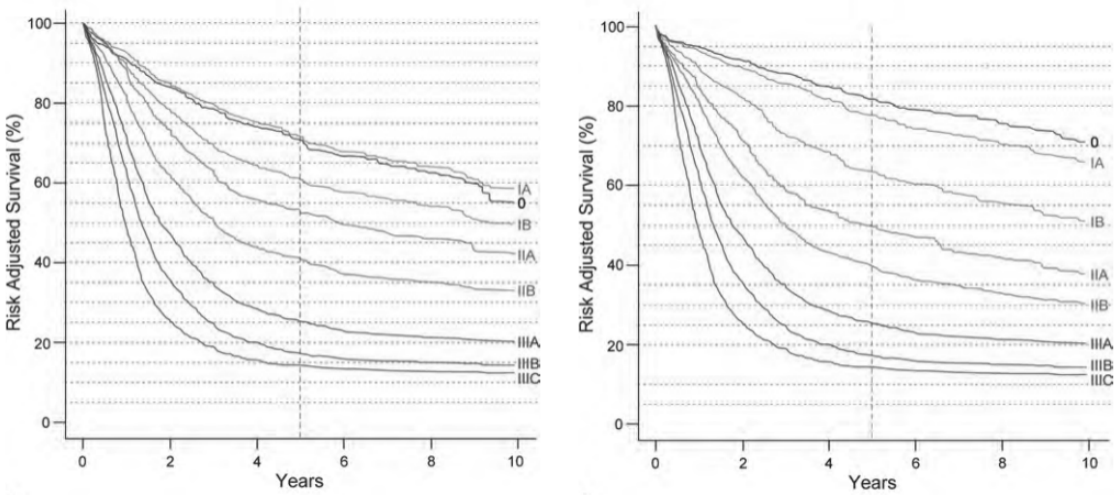


Figure 9. Survival following esophagectomy stratified by stage groupings in patients with SCC (left) and AC (right). Based on data from the Worldwide Esophageal Cancer Collaboration (WECC).[15]

1.4. Surgical techniques

1.4.1. Ivor Lewis Esophagectomy (ILE)

Middle to distal esophageal carcinoma, esophageal motility disorders requiring resection of most of the esophagus, and distal tumors arising in a long segment of Barrett's esophagus are common indications for Ivor Lewis Esophagectomy. The Ivor Lewis method gives access to perform a full thoracic lymphadenectomy and direct visualization of the thoracic esophagus. This method does not adequately remove tumors from the upper third of the esophagus, so these patients should be given the option of a total esophagectomy with a cervical anastomosis. Poor lung function, a prior thoracotomy, and fused pleural space are relative contraindications. Endoscopy should be performed by the surgeon at the time of the planned esophagectomy. Finding the tumor's proximal and distal extent is the goal. It also enables the removal of any lingering enteric materials from the stomach.[39]

The Ivor Lewis Esophagectomy has two phases: abdominal and thoracic.

The abdominal phase begins with the patient in supine position and the execution of an upper midline incision. The goal is to perform abdominal exploration in order to rule out metastatic disease, such as peritoneal implants or liver metastases, and to look for any tumor invasion into nearby structures. Up to the right crus, the gastrohepatic ligament is incised. From the right side, the hiatus and distal esophagus are dissected anteriorly and posteriorly. A Penrose drain is placed around the abdominal esophagus to help provide traction for the dissection of the distal esophagus into the mediastinum. The gastrocolic ligament is incised to access the lesser sac, making sure not to damage the right gastro-epiploic arch. An energy device is used to continue the dissection along the greater curvature towards the spleen. The short gastric vessels are divided close to the spleen and taken to the left crus. The posterior portion of the stomach is then mobilized; mobilization is sufficient when the pylorus can pass tension-free through the right crus. By moving all nodal tissue to the specimen side the left gastric artery is subsequently skeletonized and divided with a vascular stapler (Fig. 10).[39]

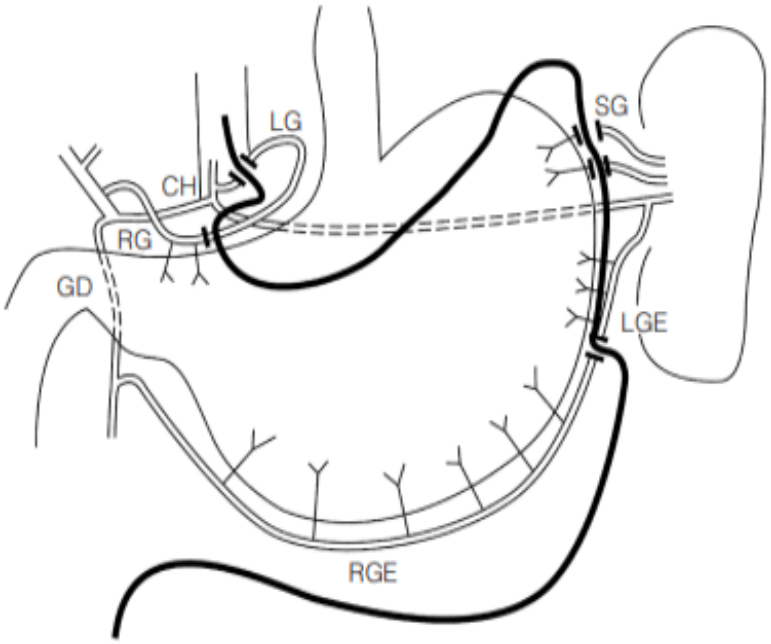


Figure 10. main arteries and points of division of the stomach in esophageal substitution.[41]

GD = Gastroduodenal

RGE = Right gastroepiploic

CH = Common Hepatic

LG = Left gastric

RG = Right gastric

SG = Short gastric

LGE = Left gastroepiploic

The gastric conduit must now be manufactured to continue the procedure. The stomach should ideally be tubularized along the larger curvature while also maintaining a width of 4-5 cm. The junction of the stomach's proximal two thirds and distal one third is typically where the stomach is transected along its lesser curvature. Grossly, one must keep their distance from the tumor at around 5 cm. The gastric tube can be pulled up into the chest because the most proximal part of the stomach is not transected (Fig. 11). Transection of the stomach is completed in the chest. [39]

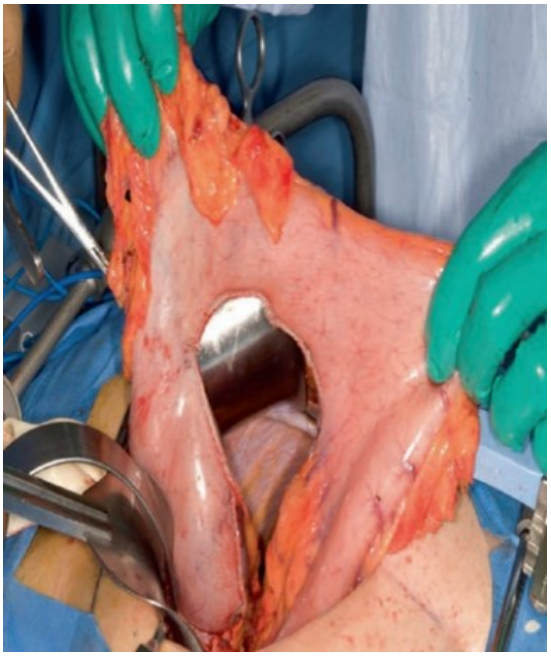


Figure 11. The gastric tube has been constructed but the specimen is still attached to the gastric tube most proximally[39]

In the thoracic phase, In order to prepare for a right thoracotomy, the patient is repositioned in the left lateral decubitus position with the right side up. Single-lung ventilation optimizes the exposure to the posterior mediastinum. A posterolateral right thoracotomy is performed sparing the serratus muscle. In the fourth or fifth interspace, the chest is accessed. The lung is retracted anteriorly and the inferior pulmonary ligament is splitted. Along the pericardium to the carina, the pleura behind the esophagus is cut. The left and right main stem bronchi are freed of the subcarinal lymph nodes. Using a vascular stapler, the azygos vein is circumferentially divided. At this point, the vagus nerve is recognized and divided to prevent traction injury to the recurrent laryngeal nerve. From the azygos vein, the pleural incision anterior to the esophagus is brought to the hiatus. All periesophageal fatty and nodal tissue is swept towards the specimen side. Circumferential dissection of the esophagus is performed from the vertebral body to the pericardium. To prevent a potential chylothorax, care should be taken to carefully clip or tie any lymphatics that are encountered. Additionally, aortic arterial branches are clipped or tied. To get an adequate margin, which is typically 5-7 cm, the esophageal dissection is moved up toward the top of the chest.[39]

Different anastomotic techniques, such as hand sewn (single layer vs. double layer), stapled (circular vs. side to side linear stapled anastomosis), and hybrid approaches have been described. However, studies have not conclusively shown that one method is superior to another. For example, a meta-analysis evaluating 12 randomized control trials showed no difference between the circular stapled anastomosis and the hand sewn technique in the incidence of anastomotic leak (RR 1.02, 95% CI 0.66-1.59) or postoperative mortality (RR 1.64, 95% CI 0.95-2.83). Comparing the circular stapled anastomosis to the hand sewn anastomosis, there was a higher incidence of anastomotic stricture (RR 1.67, 95% CI 1.16-2.42) and a shorter operating time. [40] The technique used to create the esophagogastric anastomosis is largely determined by the preference and experience of the surgeon.

To prepare the proximal esophagus for the stapled EEA anastomosis, a circular stapled anastomosis performed using an EEA stapler, a purse-string auto clamp is first applied (Fig. 12). The anvil of the EEA stapler is placed in the esophagus, and the purse-string is tightly tied around the anvil shaft (Fig. 13). The stomach is then drawn into the chest, being careful not to twist the conduit in the process. In order to insert the EEA stapler, a gastrotomy is made in the stomach area that will be resected. The conduit's vascularity, orientation, and distance from the linear staple line are taken into consideration when choosing the anastomosis site. Avoiding any abdominal redundancy or tension is essential. A stapler is used to divide the extra stomach and complete the conduit. For a frozen section of the resection margins the specimen is sent to pathology. When the anastomosis is finished, the remaining omentum is used to coat the conduit and tuck it between the staple line and the airway to avoid the possibility of a fistula. To prevent a paraconduit hernia, any extra stomach is reduced back into the abdomen and the conduit is sutured to the diaphragmatic hiatus. To lessen the strain on the anastomosis, the conduit is also fixed to the mediastinal pleura. The thoracotomy incision is closed after the anterior and posterior chest tubes have been placed, and the JP drain or posterior chest tube is positioned about 1 cm away from the stomach, parallel to it.[39]

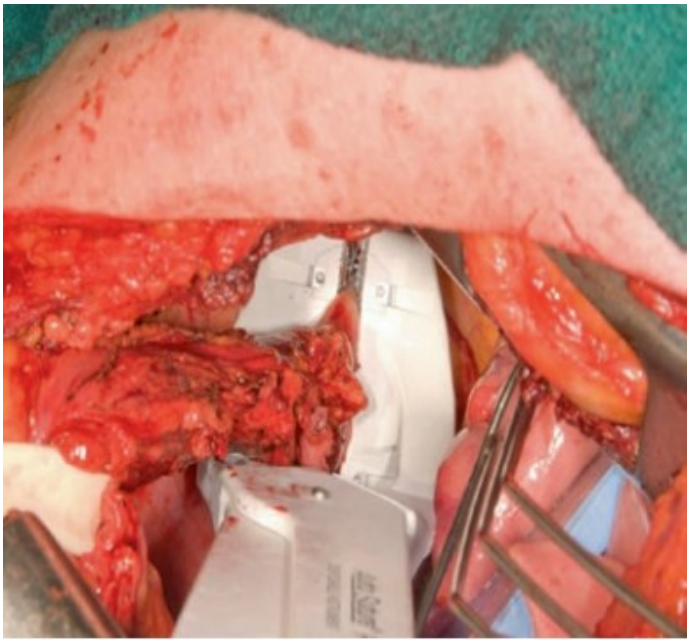


Figure 12. A purse-string is being applied at the site selected for the anastomosis using a purse-string applicator.[39]

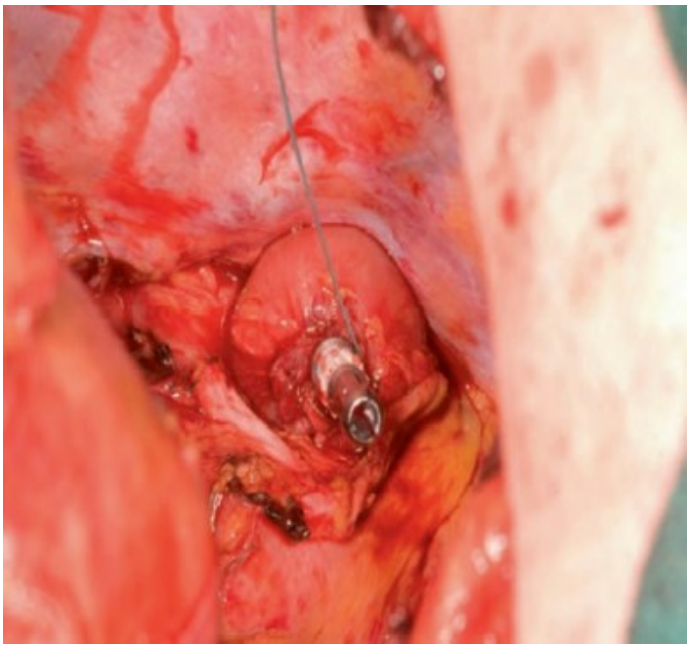


Figure 13. The anvil of the circular EEA has been placed in the lumen of the esophagus and the purse-string has been tied.[39]

1.4.2. Minimally Invasive Ivor Lewis Esophagectomy (MI-ILE)

The patient is lying on a bean bag in the supine position. The feet are taped to a padded footboard. To access the abdomen, the arms are comfortably abducted. To prevent sudden hypotension, the reverse Trendelenburg position, which is used during laparoscopy to help with upper abdomen visualization, is introduced gradually.[42]

The abdominal phase starts with the port placement. First, a port of 10 mm is placed in the clavicular midline just under the left costal margin under direct visualization. The other ports are positioned as follows: a 10 mm port in the midline just below the falciform ligament, a third 10 mm port in the right flank, and a 5 mm port in the right upper quadrant so that instruments will have an easy trajectory under the liver and falciform ligament and towards the hiatus. This is done after abdominal insufflation with CO2 at 15 mmHg. For the assistant, an additional 5 mm port can be positioned in the left upper quadrant. To elevate the left lobe of the liver and reveal the hiatus, a Nathanson liver retractor is positioned just below the xiphoid bone (Fig. 15). [42]

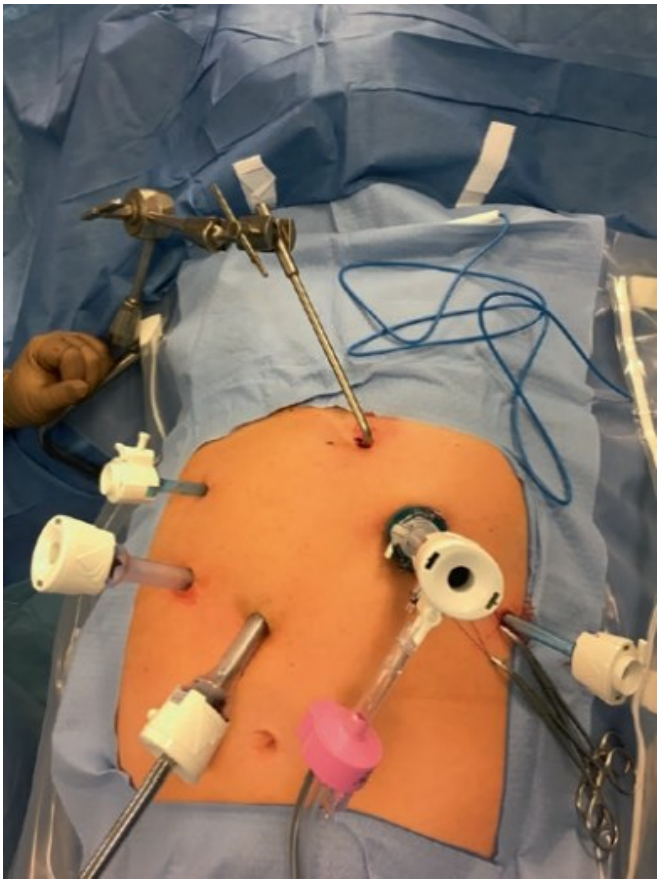


Figure 15. Port placement of MI-ILE during abdominal phase.[42]

The gastro-hepatic ligament is first divided, and then the dissection moves upward until it reaches the right crus. To fully dissect the associated nodes, the left gastric, splenic, and common hepatic arteries must be identified. The hepatic artery is recognized as the dissection begins at the superior aspect of the pancreas. This artery is skeletonized superiorly to the takeoff of the left gastric and splenic arteries. The lymph nodes are swept upward into the specimen once the left gastric artery has been located so that the artery and vein can be split at their origin with a vascular stapler. The celiac artery nodes located between the left gastric artery stump and the base of the diaphragmatic crus can be reached by retracting the stomach anteriorly. The dissection is carried on, reaching the base of the hiatus and the posterior mediastinum and separating the left crus from its phrenoesophageal attachments toward the angle of His. Dissecting the greater curvature of the stomach now is the focus. The gastrocolic ligament is clearly displayed by a gentle anterior and right retraction of the stomach. For the gastric conduit to be perfused, the right gastroepiploic artery must be preserved. The gastrocolic ligament is divided along the greater curve toward the fundus, keeping far away from this artery. When the gastroepiploic artery terminates it is safe to bring the dissection closer to the stomach wall. By doing this, it is possible to divide the short gastric arteries, leaving a long stump on the splenic side. As mobilization moves toward the previous dissection along the left crus, care is taken to avoid damaging the spleen. Following complete fundus mobilization, the gastrocolic ligament is divided further caudally in the direction of the pylorus. Fully dividing these attachments between the distal stomach and the colon lessens strain on the anastomosis and aids in lowering the risk of colonic herniation via the hiatus. The colon should be entirely separate from the stomach and proximal duodenum, and the pylorus should be freely mobile. A Penrose drain is passed around the distal esophagus and fastened with a locking clip to create a mobile handle before the trans hiatal esophageal dissection of the esophagus can begin. A transhiatal dissection is carried out as high as possible, roughly to the level of the inferior pulmonary vein, using the drain to help with retraction. The specimen has to be kept en bloc with the periesophageal lymph nodes, including the nodes anterior to the back of the pericardium. To start the tubularization of the conduit, a point on the lesser curve just cranial to the pylorus is chosen. Then, the separation of the conduit from the specimen begins moving upwards toward the fundus. Stretching the stomach from the

fundus' tip is imperative in order to create a conduit that is 4-5 cm wide and keeping the staple line as straight as possible. So that the specimen and conduit can later be delivered into the chest together and in the right orientation, the staple line has to stop about 3 cm near the fundus. Finally, a Penrose drain is passed through the hiatus where it will later be retrieved via the chest. The liver retractor is removed, hemostasis ensured and all port sites closed in the standard fashion.[42]

The thoracic phase starts with the patient positioned in the left lateral decubitus and ventilated with single-lung ventilation. The access to the chest is mediated by the insertion under direct visualization of a 10 mm optical port in the posterior axillary line at the level of the seventh intercostal space. A 10 mm camera port is put into place next, in the ninth intercostal space just posteriorly to the first port. After it, a 10 mm port in the fourth or fifth intercostal space in the mid-axillary line, and a 5 mm port in the seventh intercostal space between the scapula and the spine are positioned (Fig. 16).[42]

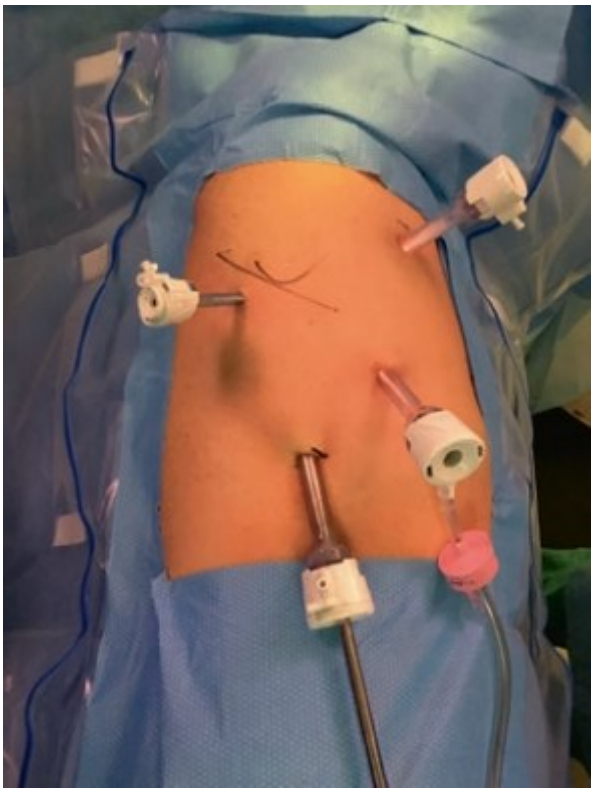


Figure 16. Port placement of MI-ILE during thoracic phase.[42]

After chest insufflation with CO2 at a pressure of 8 mmHg the thoracoscopic dissection starts. The first action is the division of the inferior pulmonary ligament and the removal of the associated lymph nodes. The procedure continues with the incision of the mediastinal pleura anterior to the esophagus in the direction of the azygos vein, which is then divided using a vascular stapler. The dissection is then brought back down to the diaphragm where the transhiatal dissection through the abdomen is encountered. The Penrose drain put into place earlier has to be located and used as a retraction handle. The dissection of the esophagus out of its bed in the mediastinum can be completed proceeding again superiorly toward the azygos vein. Identification and clipping of arterial branches from the aorta and lymphatic branches from the thoracic duct is necessary to avoid post-operative complications such as chylothorax. The subcarinal nodes are moved into the specimen part being careful to avoid damaging the airway in order to prevent the formation of a tracheoesophageal fistula. In addition, to prevent ischemia, the bronchial artery branches supplying the airway should be preserved. The esophagus is then dissected beneath the pleura for 2 cm past the point where the pleura was divided at the level of the azygos vein; this way the preserved membrane will support the final anastomosis. A linear stapler is used to divide the esophagus at the level of the azygos vein: the anastomosis is placed at least at this level to avoid redundant gastric conduit in the abdomen, which can cause reflux. The anesthesiologist will then carefully advance an oral anvil (Orvil, Medtronic, Minneapolis, MN) for the circular stapler. To help guide the tube and maintain a horizontal staple line, the surgeon should grasp the staple line on both sides. Once the tube's tip is visible, a tiny hole is made just above the staple line's center by cauterizing the area. As the anesthesiologist moves the anvil over the palate's back, the tube's end is pulled through the opening that was just created. For the conduit and the specimen to be delivered into the chest, the distal esophagus is gently pulled upward. The conduit's staple line needs to be perfectly straight and facing the patient's right. With care to maintain an adequate margin and leave space for the insertion of the circular stapler to form an end-to-side esophagogastric anastomosis, the specimen is separated from the conduit using a linear stapler. The specimen is taken out in a retrieval bag and sent for intraoperative evaluation of the proximal and distal resection margins. Only after it is certain that the margins are unaffected the anastomosis is carried out. The conduit's proximal tip is

grabbed and split open parallel to the staple line with cautery, making room for the circular stapler to be inserted. The stapler is inserted and the anastomosis is performed with no tension and in an area of good conduit perfusion, leaving the greater curvature vessels on the tracheal side of the anastomosis in order to protect the airways in case of leak.[44] The anastomosis may be exposed to the formation of dog-ears at the intersection of the circular plane of the stapler and the linear staple line of the esophageal stump, increasing the risk of anastomotic leak. In order to prevent the occurrence of clinically relevant anastomotic leaks, Valmasoni et al. described a modified circular stapled technique in a small case series of patients that consists of folding the linear esophageal transection line with a stitch around the anvil shaft, to include the staple line in the resection during the EEA firing (Fig 17, 18, 19, 20, 21).[43] After the stapler is taken out, a linear stapler is used to transect the conduit's opened proximal end. To prevent ischemia, the anastomosis and the gastric staple line must be at least 1-2 cm apart. The superior mediastinal pleura is now allowed to cover the anastomosis as it retracts. With the aid of absorbable sutures, the conduit is fastened to the pleura. Omentum or pericardial fat are wrapped around the vertical staple line of the conduit to separate it from the airway. A nasogastric tube is then inserted by the anesthesiologist until the tip is inside the distal conduit. Finally, non-absorbable suture is used to anchor the conduit to the diaphragm at the hiatus in order to help prevent paraconduit herniation. A single straight chest tube is put into place and the lung is re-expanded. The conventional method is used to close the incisions.[42]

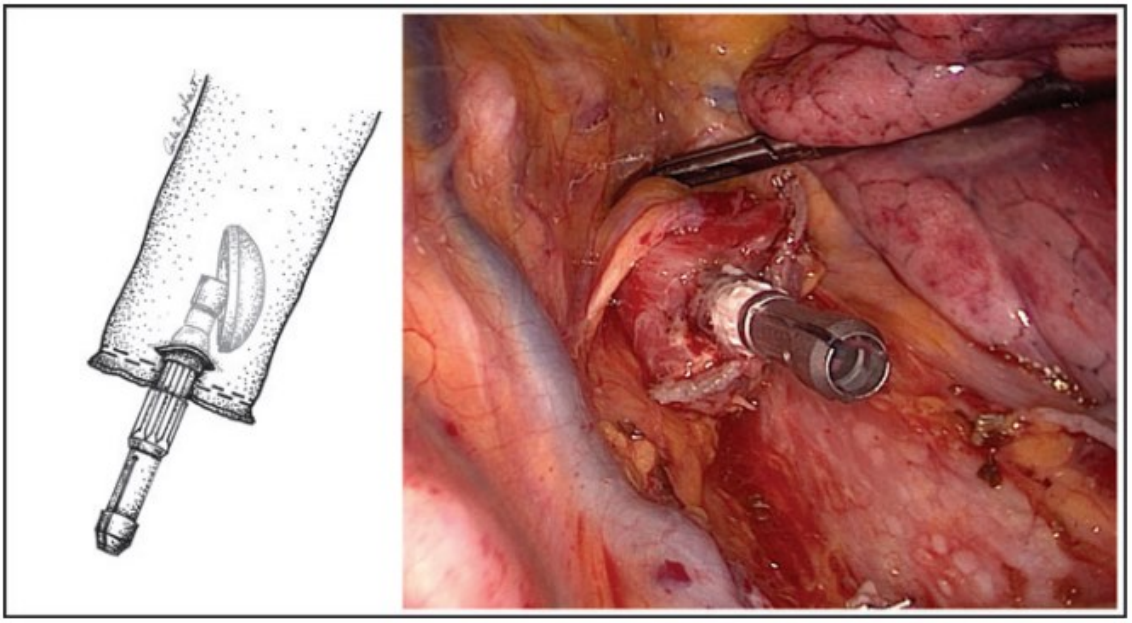


Figure 17. The anvil is passed through a hole above the staple line.
Illustration: Carla Brighenti.[43]

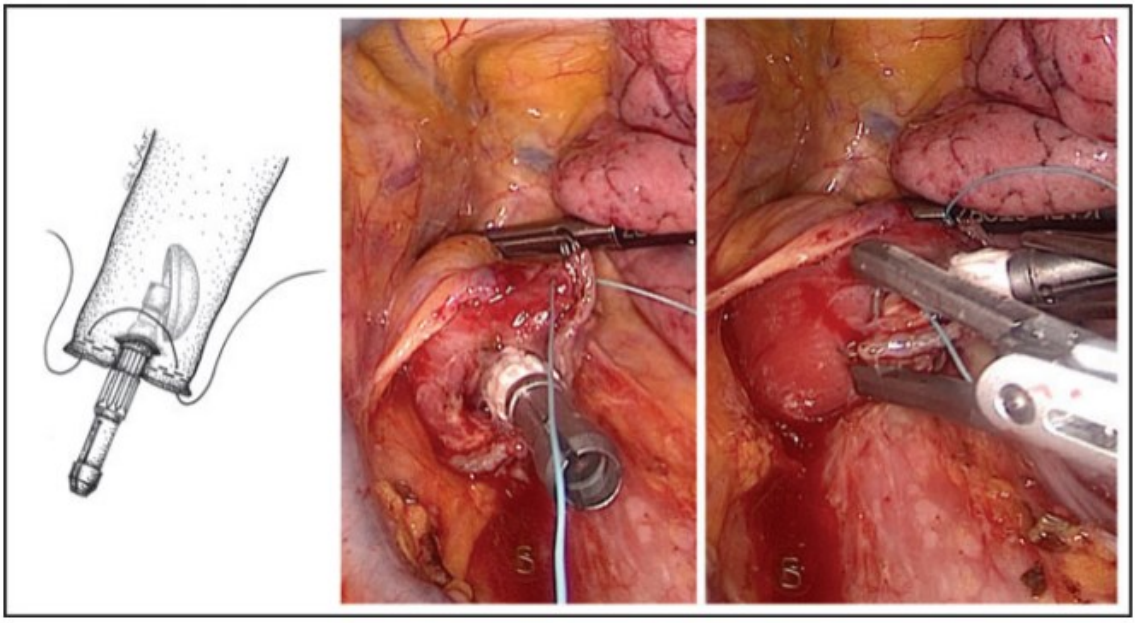


Figure 18. Using a stitch the staple line is wrapped around the anvil shaft.
Illustration: Carla Brighenti.[43]

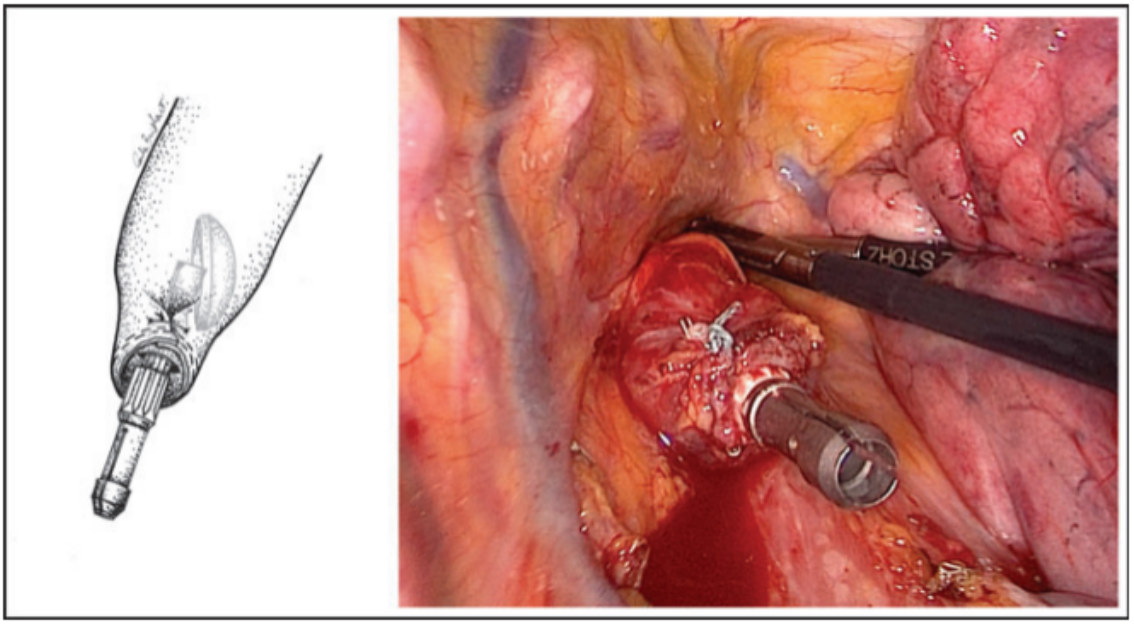


Figure 19. Staple line wrapped around the anvil shaft.
Illustration: Carla Brighenti.[43]

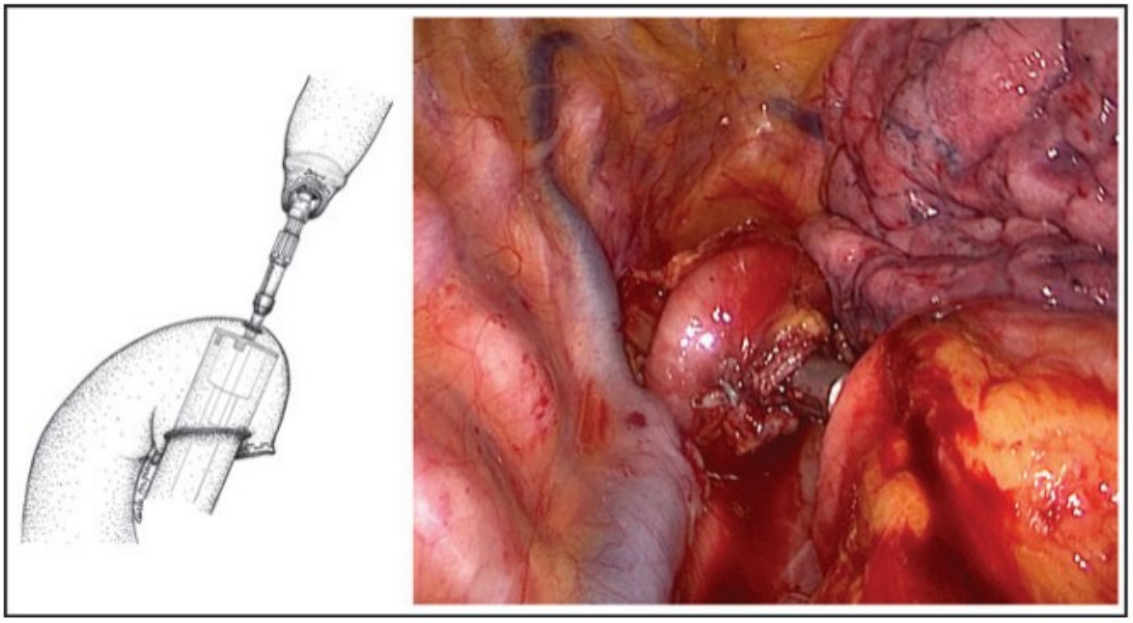


Figure 20. The stapler and the anvil are engaged.
Illustration: Carla Brighenti.[43]

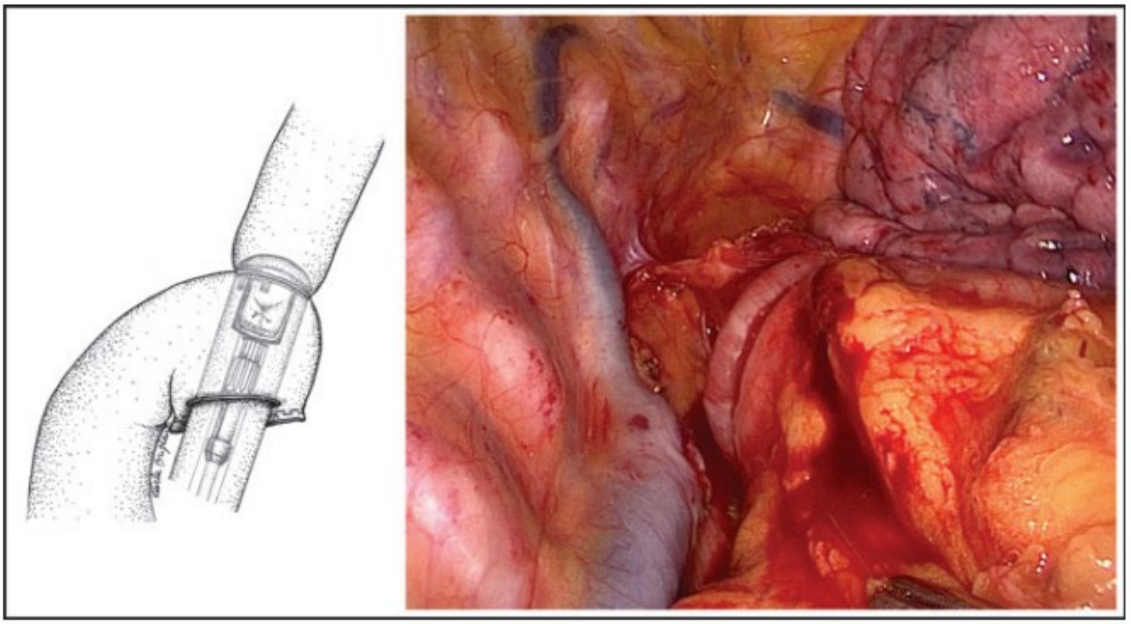


Figure 21. The anastomosis is performed with no dog-ears.
Illustration: Carla Brighenti.[43]

1.5. Minimally Invasive compared to Open Esophagectomy

The Minimally Invasive Ivor Lewis Esophagectomy (MI-ILE) procedure is technically difficult and demands advanced thoracoscopy and laparoscopy skills. With practice, the procedure can be carried out with excellent patient outcomes in terms of perioperative morbidity and oncologic efficacy while only slightly lengthening the surgical time when compared to open approaches.[44,47,48,49] The minimally invasive approach causes less pain and blood loss and has fewer pulmonary complications because open incisions are avoided, particularly with the thoracotomy.[45,47,48,50,51] The length of stay is consequently shortened.[47,50,51] Anastomotic leak rate is similar between the approaches,[45,47,59-51] but some studies have shown a slight but significant increase in the need for reoperation in comparison to open esophagectomy.[48,49] Importantly, with minimally invasive esophagectomy, oncologic outcomes such as completeness of resection, number of lymph nodes removed, recurrence, and 3- and 5-year survival appear equivalent, if not improved.[45,50,51] Potential oncologic benefits of the minimally invasive approach include less immune dysfunction (related to surgical stress and blood transfusion) and improved visualization for more complete lymphadenectomy (particularly in obese patients).[42] The surgical and oncological outcomes of the above studies are summarized in Tab. IV.[44] In the end, the surgeon's preference and experience will determine the approach. Beyond a patient's tolerance for pneumoperitoneum and a few factors like prior abdominal or thoracic surgery or bulky disease, there are no formal contraindications to a minimally invasive approach.[46]

Table IV. Best operative approach for selected surgical and oncologic outcomes (adjusted).[42]

	Biere[47]	Takeuchi[48]	Sihag[49]	Tapias[50]	Palazzo[51]
Length of stay	MIE	ND	MIE	MIE	MIE
ICU length of stay/ ventilation	ND	MIE	ND	MIE	-
Operative time	OE	OE	OE	ND	-
Blood loss/ transfusion	MIE	MIE	MIE	MIE	MIE
Anastomotic leak	ND	ND	ND	ND	ND
Recurrent nerve injury	MIE	OE	-	ND	-
Superficial/ wound infection	-	MIE	MIE	-	-
pneumonia/ empyema	-	MIE	OE	ND	MIE
Pain	MIE	-	-	-	-
Need for reoperation	ND	OE	OE	-	-
Margin	ND	-	-	ND	ND
Nodes removed	ND	-	-	ND	MIE
operative/30 day mortality	ND	ND	ND	ND	ND

Minimally Invasive Esophagectomy (MIE) = Blue

Open Esophagectomy (OE) = Yellow

No difference (ND) = Gray

2. AIM OF STUDY

The purpose of this study is to evaluate the safety and efficacy of implementing a totally minimally invasive esophagectomy program for cancer in a high-volume center. In addition, it aimed to evaluate the impact of the learning curve on perioperative and oncologic outcomes. Survival and disease-free survival were included as secondary endpoints.

3. MATERIALS AND METHODS

3.1. Study design

This study is a prospective non-randomized control study from a single center. From the start of the minimally invasive program in June 2018 to October 2022, data were gathered on all consecutive patients who underwent elective Ivor Lewis esophagectomy at the Upper G.I. Surgery Unit "General surgery I" of Padova University. Patients undergoing Minimally Invasive Ivor Lewis Esophagectomy were assigned to the MIE group ("minimally invasive esophagectomy"), those undergoing Open Ivor Lewis Esophagectomy to the OE group ("open esophagectomy"). By comparing the perioperative and oncological outcomes of patients who underwent MIE to those of patients treated with OE during the same period, we evaluated the safety and efficacy of the minimally invasive approach in the treatment of esophageal cancer. Subsequently, the MIE group was divided into two groups: Early Experience ("EE") and Late Experience ("LE") group. By comparing the perioperative and oncological outcomes between the two groups we evaluated the presence and the impact of a learning curve.

3.2. Patients selection

3.2.1. Inclusion criteria

Patients had to satisfy each of the following requirements in order to be considered for the analyses:

- Age 18 or older.
- Histological diagnosis of esophageal carcinoma, adenocarcinoma or squamous cell cancer.
- Ivor Lewis Esophagectomy (open or minimally invasive) with the goal of curing the disease (cT_{1-4} N_{0-3} M_0).
- 90 days of follow-up or more after surgery.

3.2.2. exclusion criteria

Patients who met one of the following criteria were not included in the analyses:

- Benign esophageal disease.
- Surgery performed in emergency or urgent settings.
- underwent surgical techniques other than Ivor Lewis Esophagectomy.

3.3. Study data

3.3.1. Preoperative evaluation

The preoperative assessment was performed during a surgical visit to gather the patients' physiological anamnesis, prior medical and surgical histories, and clinical examinations. Additionally, we registered anthropometric information like height, weight, and BMI. To assess the presence of comorbid diseases, we used the Charlson Comorbidity Index (CCI) score (ICD-9-CM adaptation).[52] We used the ECOG (Eastern Cooperative Oncology Group performance status)[53] scale to assess how the disease affects the patients' abilities to perform daily activities. Laboratory tests, electrocardiogram, pulmonary function tests, spirometry, and transthoracic echocardiogram were eventually included in the pre-operative investigations. Preoperative anesthesiologic evaluations were performed on all patients in order to evaluate the perioperative risks using the ASA Physical Status Classification System. [54]

3.3.2. Staging

Endoscopic ultrasonography and esophagogastroduodenoscopy with biopsy were the procedures used to identify esophageal cancer. The histology was categorized according to World Health Organization (WHO) criteria.[55] To find mutations that could be treated with specific systemic treatments, additional genetic tests were carried out.
The presence of metastases, lymph node involvement, and wall infiltration were assessed using PET-CT and CT scans of the neck, chest, and abdomen.
All patients with SCC and patients with middle thoracic AC (above the carina level) underwent an ORL visit and bronchoscopy to determine the involvement of airways.

According to the staging system developed by the AJCC (8th edition), esophageal cancer was staged.[17]

3.3.3. Neoadjuvant therapy

Neoadjuvant therapy was taken into consideration for each patient after a multidisciplinary evaluation. According to the cancer's stage, location, histological type, and the patient's performance status and comorbidities, preoperative treatments were recommended. According to institutional-specific protocol, all patients with stage IIb and stage III cancer and good performance status underwent preoperative chemo-radio-therapy or perioperative chemotherapy with neoadjuvant intent. Following neoadjuvant therapy, the cancer response was assessed using esophagogastroduodenoscopy with biopsy, contrast CT, and PET-CT. The restaging made use of the classification by AJCC staging system (8th edition).[17] A multidisciplinary team assessed surgical indication and neoadjuvant therapy response.

3.3.4. Surgical treatment

Ivor Lewis esophagectomy, either open or minimally invasive, was used to remove the tumors. The surgeon's preference, the clinical characteristics of the patient, and the stage of the tumor disease were taken into account when deciding which approach to use prior to surgery (especially in the early experience). Patients who had undergone extensive abdominal or thoracic surgery in the past were not eligible for the minimally invasive approach. Standard two-field lymphadenectomy was performed, including the posterior mediastinal, subcarinal, and periesophageal lymph nodes in the thoracic field. The lymphadenectomy in the abdominal field included celiac artery lymph nodes, paracardial nodes, those along the small curvature and at the origin of hepatic and splenic artery. With a few minor adjustments due to laparoscopic specific variation, the same technique in both the open and minimally invasive approach was used. A mechanical circular end-to-side esophagogastric anastomosis was most often done. During open surgery, the anvil was introduced in the esophagus performing a hand sewn purse string, while, in minimally invasive esophagectomy, introducing an OrVil using

the transoral route was preferred. Pylorus digital dilation was most often performed during open surgery, while, in minimally invasive esophagectomy, the pyloric drainage procedure wasn't almost never done. In both techniques, jejunostomy and the ligation of the thoracic duct weren't routinely performed.

In the abdominal phase of the minimally invasive procedure, five laparoscopic ports were put into place and a steep reverse Trendelenburg position was established. The tumor resection was carried on only if no signs of metastatic disease were found during the initial examination of the abdominal cavity. The celiac trunk was made visible by opening the gastro-hepatic ligament. Complete lymphadenectomy around the hepatic, left gastric, and proximal splenic arteries was carried out using an ultrasonic dissector. Depending on the size of the vessels, the left gastric vessels were divided at their origin using a vascular stapler or Hem-o-locks. With an ultrasonic dissector positioned just distal to the gastroepiploic arcade, the gastro-colic ligament was divided from right to left, and then up to the short gastric vessels. The diaphragm and pancreatic anterior surface attachments to the stomach were removed, leaving the stomach completely free. The pylorus was brought to the base of the diaphragmatic crus using a limited Kocher maneuver. The right gastroepiploic vessels were carefully protected during this maneuver because they support the vascularization of the gastric conduit. The esophagus was then dissected from the diaphragmatic crus up to the lower mediastinum. This step of the procedure was saved until the end of the abdominal portion of the surgery because it could accidentally violate the right or left pleura, resulting in the patient temporarily experiencing hemodynamic instability. A Penrose drain was used to encircle the esophagus to aid in the thoracic esophageal dissection. Using three to four firings of a linear tri-stapler, a gastric conduit was created. In order to prevent excessive conduit redundancy, special attention was paid to the gastric conduit's size (four to five cm wide). To make gastric retrieval from the chest easier and prevent the conduit from twisting, the last three cm of the conduit were left undivided. One abdominal Penrose Drain twelve French wide was positioned under the liver, behind the gastric conduit, and up to the splenic loggia.

The patient was then turned to the left lateral decubitus position and a standard right video-assisted thoracoscopic surgery (VATS) was performed. Four thoracoscopy ports were put into place and CO2 was insufflated inside the thorax maintaining a pressure of

8 mmHg. The lung was retracted anteriorly and laterally so that the inferior pulmonary ligament could be accessed and divided. The azygos vein was divided with an Endo-GIA vascular stapler. The posterior mediastinal pleura was opened just above the hiatus, and the Penrose around the esophagus was retrieved. Using the Penrose drain to help with exposure and traction, the esophagus was mobilized en-bloc with the periesophageal soft tissues from the diaphragm up to the level of Azygos vein. A complete infra-carinal lymphadenectomy was routinely performed. The esophagus was transected just below the thoracic inlet with a linear stapler. A mini-thoracotomy was performed by extending the inferior and medial port site of five cm. A wound protector was applied. In order to prevent conduit twisting, the gastric conduit was lifted into the chest while maintaining the correct orientation. A twenty five mm EEA circular stapler (Covidien, MN, Minneapolis, USA) together with a twenty five mm Orvil™ (Covidien) were used to complete the intrathoracic anastomosis. The Orvil™ was passed through the patient's mouth and down into the esophageal stump. A small opening was made just next to the staple line, thus enabling the retrieval of the device from the thorax via the extraction site. A gastrotomy was performed and the stapler was introduced via mini-thoracotomy in the gastric fundus. The spike of the stapler was used to pierce the greater curvature just proximally to the gastroepiploic arcade. The anvil and stapler were engaged, and the stapler fired to complete the anastomosis. The tip of the stomach fundus was then resected using a EndoGIA linear stapler, making sure to leave at least one cm of tissue between the staple line and the anastomosis. The specimen was then retrieved. The gastric conduit was sutured to the mediastinal pleura in order to relieve any possible anastomotic tension. If feasible, an omental wrap was put around the anastomosis, between the conduit and the airways, in order to protect the anastomosis Posteriorly. A nasogastric tube was inserted within the gastric conduit and a twenty eight French Argyle chest tube was left in the pleural apex at the end of the procedure.

3.3.5. Surgical outcomes

The surgical reports were used to record the specifics of the surgical operations. The following data were registered:

- Duration of the surgical procedure, calculated from the beginning of the abdominal to the end of thoracic phase.
- Duration of abdominal and thoracic phases.
- Conversion of the minimally invasive to the open procedure, either abdominal or thoracic.
- Reason why the minimally invasive procedure was converted to open.
- EEA circular stapler diameters.
- anastomosis reinforcement.

3.3.6. Pathological examination

Pathologists with expertise in upper gastrointestinal malignancies processed and examined each specimen. The classification by AJCC staging system (8th edition) was used to categorize esophageal carcinoma.[17] The surgical radicality was defined according to the College of American Pathologists esophageal cancer protocol.[56] The pathological reports were used to register the details of the pathological examination:

- Involvement of proximal, distal and circumferential resection margins.
- Total number of lymph nodes harvested.
- Total number of lymph nodes harvested from the abdominal and thoracic fields.
- Total number of lymph nodes found positive.
- Total number of lymph nodes found positive in the abdominal and thoracic fields.

3.3.7. Post-operative care

The institution's protocol of Padova University hospital states that patients under the age of 70, those without pre-anesthesia medical conditions, and those with mild systemic diseases (ASA 1 or 2) do not require postoperative ICU monitoring. Following surgery, the patients with low anesthesiologic risk were monitored in a post-anesthesia care unit (PACU). The patients' health records were used to report data regarding the post-operative care parameters:

- Total number of days in intensive care unit during hospitalization.
- Hospital stay (from the day of the surgery to the day of discharge).
- Total number of blood units transfused.

3.3.8. Early complications

The postoperative complications were classified according to the Esophagectomy Complications Consensus Group (ECCG) classification (Fig. 22, Fig. 23).[57] The complications taken into consideration emerged throughout the patient's hospital stay. Anastomotic leakages were evaluated if they were identified using any one of the following methods, individually or in combination: endoscopy, oral and intravenous contrast CT scan, radiological control with iodinated contrast or reoperation. According to Clavien Dindo classification of Surgical Complications, the perioperative complications severity were recorded (Fig. 24).[64]

Pulmonary

- Pneumonia (Definition: American Thoracic Society and Infectious Diseases Society of America)[58]
- Pleural effusion requiring additional drainage procedure
- Pneumothorax requiring treatment
- Atelectasis mucous plugging requiring bronchoscopy
- Respiratory failure requiring reintubation
- Acute respiratory distress syndrome (Berlin Definition)[59]
- Acute aspiration
- Tracheobronchial injury Chest tube maintenance for air leak for >10 d postoperatively

Cardiac

- Cardiac arrest requiring CPR
- Myocardial infarction (Definition: World Health Organization)[60]
- Dysrhythmia atrial requiring treatment
- Dysrhythmia ventricular requiring treatment
- Congestive heart failure requiring treatment
- Pericarditis requiring treatment

Gastrointestinal

- Esophago-enteric leak from anastomosis, staple line, or localized conduit necrosis.
- Conduit necrosis/failure.
- Ileus defined as small bowel dysfunction preventing or delaying enteral feeding
- Small bowel obstruction
- Feeding J-tube complication
- Pyloromyotomy/pyloroplasty complication
- Clostridium difficile Infection
- Gastrointestinal bleeding requiring intervention or transfusion
- Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 d postoperatively
- Pancreatitis
- Liver dysfunction

Figure 22a. Complications basic platform (adjusted).[57]

Urologic

- Acute renal insufficiency (defined as doubling of baseline creatinine)
- Acute renal failure requiring dialysis
- Urinary tract infection
- Urinary retention requiring re-insertion of urinary catheter, delaying discharge, or discharge with urinary catheter

Thromboembolic

- Deep venous thrombosis
- Pulmonary embolus Stroke (CVA)
- Peripheral thrombophlebitis

Neurologic/psychiatric

- Recurrent nerve injury
- Other neurologic injury
- Acute delirium (Definition: Diagnostic and Statistical Manual of Mental Disorders, 5th ed)[61]
- Delirium tremens

Infection

- Wound infection requiring opening wound or antibiotics
- Central IV line infection requiring removal or antibiotics
- Intrathoracic/intra-abdominal abscess
- Generalized sepsis (Definition: CDC)[62]
- Other infections requiring antibiotics

Wound/diaphragm

- Thoracic wound dehiscence
- Acute abdominal wall dehiscence/hernia
- Acute diaphragmatic hernia

Other

- Chyle leak
- Reoperation for reasons other than bleeding, anastomotic leak, or conduit necrosis
- Multiple organ dysfunction syndrome (Definition: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee)[63]

Figure 22b. Complications basic platform (adjusted).[57]

Anastomotic Leak

Defined as: Full thickness GI defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification

Type I: Local defect requiring no change in therapy or treated medically or with dietary modification

Type II: Localized defect requiring interventional but not surgical therapy, for example, interventional radiology drain, stent or bedside opening, and packing of incision

Type III: Localized defect requiring surgical therapy

Conduit Necrosis

Type I: Conduit necrosis focal Identified endoscopically Treatment—Additional monitoring or non-surgical therapy

Type II: Conduit necrosis focal Identified endoscopically and not associated with free anastomotic or conduit leak Treatment—Surgical therapy not involving esophageal diversion

Type III: Conduit necrosis extensive Treatment—Treated with conduit resection with diversion

Chyle Leak

Type I: Treatment—enteric dietary modifications

Type II: Treatment—total parenteral nutrition

Type III: Treatment—interventional or surgical therapy

Vocal Cord Injury/Palsy

Defined as: Vocal cord dysfunction post-resection. Confirmation and assessment should be by direct examination

Type I: Transient injury requiring no therapy Dietary modification allowed

Type II: Injury requiring elective surgical procedure, for example, thyroplasty or medialization procedure

Type III: Injury requiring acute surgical intervention (due to aspiration or respiratory issues)

Figure 23. Complications basic platform definitions (adjusted).[57]

Grade I

Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions

Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy.

This grade also includes wound infections opened at the bedside

Grade II

Requiring pharmacological treatment with drugs other than such allowed for grade I complications

Blood transfusions and total parenteral nutrition are also included

Grade III

Requiring surgical, endoscopic or radiological intervention

Grade IIIa

Intervention not under general anesthesia

Grade IIIb

Intervention under general anesthesia

Grade IV

Life-threatening complication requiring IC/ICU management (including CNS complications)

Grade IVa

Single organ dysfunction (including dialysis)

Grade IVb

Multiorgan dysfunction

Grade V

Death of a patient

Figure 24. Clavien Dindo classification of surgical complications severity.[64]

3.3.9. Follow-up and survival

Routine follow-up was typically scheduled for one month, three months, six months, and twelve months after hospital discharge during the first year; every six months for the next 5 years, and finally yearly. At the one-month control, an oral contrast radiography was often evaluated to look for potential anastomosis stenosis and delayed stomach emptying. Chest-abdomen contrast enhanced CTs were performed at three months and six months after discharge during the first year; every 6 months for the first 5 years, and then annually. EGDS tests were done at six months and then annually. From the follow-up visit reports the following data were recorded:

- 90-day readmission
- 90-day mortality
- Recurrence and data of recurrence
- Mortality
- Cause of death

3.4. Statistical analyses

Intention-to-treat analysis was used to conduct the statistical analyses. The continuous variables are presented as mean ± standard deviation (SD), the categorical variables as size and frequency. Both the Pearson chi-squared test and the Student's t test were used to examine correlations. P values less than 0.05 were considered to be significant. Kaplan meier analyses have been conducted on survival and disease-free survival. Cumulative sum (CUSUM) analyses have been used to calculate the learning curves. GraphPad Prism (Version 9.5.1 for Windows) and Jamovi (Version 2.3.23 for Windows) were used for all statistical analyses.

4. RESULTS

4.1. Population

A total number of 208 patients were submitted to Ivor Lewis Esophagectomy during the inclusion period (from June 2018 to October 2022). The minimally invasive approach was chosen for 61 patients, 9 patients underwent hybrid Ivor Lewis Esophagectomy (they weren't included in the analyses) and 138 patients underwent traditional Ivor Lewis Esophagectomy. The patients' data recorded before the operation day are summarized in Tab. V.

Table Va. patient's characteristics.
OE GROUP = Open Esophagectomy group
MIE GROUP = Minimally Invasive Esophagectomy group

VARIABLES	OE GROUP	MIE GROUP	P value
Sex			ns
male	106 (76,8%)	54 (88,5%)	
female	32 (23.2%)	7 (11,5%)	
Age (years)	63,8 ± 11,1	60,1 ± 10,7	**0,030**
Charlson Comorbidity Index	4,9 ± 1,9	4,1 ± 1,6	**0,005**
BMI (Kg/m^2)	24,8 ± 5,0	25,4 ± 4,3	ns
ASA grade			ns
1	0 (0%)	1 (1,7%)	
2	70 (50,7%)	39 (63,9%)	
3	68 (49,3%)	21 (34,4%)	
Tumor histology			ns
AC	95 (68,8%)	48 (78,7%)	
SCC	43 (31,2%)	13 (21,3%)	

Table Vb. patient's characteristics.

VARIABLES	OE GROUP	MIE GROUP	P value
Clinical stage			ns
1	11 (8,0%)	4 (6,6%)	
2	29 (21,0%)	9 (14,8%)	
3	90 (65,2%)	48 (78,7%)	
4	8 (5,8%)	0 (0%)	
Neoadjuvant therapy			ns
no	32 (23,2%)	11 (18,0%)	
CRT	61 (42,2%)	27 (44,3%)	
CT	44 (31,9%)	23 (37,7%)	
RT	1 (0,7%)	0 (0%)	

The patient population consisted mainly of males (80,4%) with no statistical difference between the OE and MIE groups, while there was statistical difference between the mean age: 63,8 ± 11,1 years in the OE group and 60.1 ± 10,7 years in the MIE group (P value=**0,030**). The Charlson Comorbidity Index was significantly higher in the OE group compared to the MIE group, Respectively 4,9 ± 1,9 vs 4,1 ± 1,6 points on average (P value=**0,005**). No statistical differences were found comparing the BMI and the ASA grade, even if a trend towards an inferior ASA grade can be noticed in the MIE group. The number of adeno- and squamocellular- carcinomas was evenly distributed in the two groups. The clinical stage was compared between the OE and SCC groups and no statistical differences were found between the two groups. Neoadjuvant therapy had been performed homogeneously between the two groups, with 44,2% of patients receiving chemoradiation therapy, 33,7% of patients receiving chemotherapy, 21,6% of patients not receiving any preoperative treatment and only 1 patient (0,5%) receiving preoperative radiotherapy.

4.2. Surgical outcomes

During the inclusion period, the minimally invasive approach was chosen for 61 patients, and 138 patients underwent traditional Ivor Lewis Esophagectomy. Conversion to open procedure was necessary in 8 (13,1%) of the 61 patients: 2 (3,3%) during abdominal phase, 5 (8,2%) during thoracic phase, and 1 (1,6%) during both. These patients were converted because of technical difficulties (e.g. presence of fibrotic adhesions or bulky tumors), never because of intraoperative complications or anesthesiological needs. The other data recorded are reported in Tab. VI.

Table VI. Surgical Outcomes

VARIABLES	OE GROUP	MIE GROUP	P value
Anastomosis reinforcement	24 (17,4%)	47 (77,0%)	**<0,001**
Diameter circular stapler (mm)			**<0,001**
21	2 (1,4%)	0 (0%)	
25	70 (50,7%)	58 (95,1%)	
28	63 (45,7%)	3 (4,9%)	
29	1 (0,7%)	0 (0%)	
31	2 (1,4%)	0 (0%)	
Total duration (min)	295 ± 62,2	363 ± 56,1	**<0,001**
Abdominal duration (min)*	158 ± 46,9	183 ± 40,6	**0,006**
Thoracic duration (min)*	162 ± 36,6	179 ± 30,5	**0,018**

**The Abdominal Duration and Thoracic Duration fields consider only a portion of the patients enrolled in the study, 44 for the OE group and 49 for the MIE group, respectively; data for the remaining patients were missing from the anesthesiology reports.*

Anastomosis reinforcement was performed more during the minimally invasive approach than the open approach (P value < 0,001), in the Open Esophagectomy group it was done in 24 (17,4%) patients, while in the Minimally Invasive Esophagectomy group was done in 47 (77,0%) patients. The diameter of the Circular Stapler was significantly smaller in the MIE group than in the OE group (P value < 0,001). 95,1% of MIEs involved a 25-mm diameter circular stapler, while OEs mainly involved 25-mm (50,7%) and 28-mm (45,7%) diameter circular staplers. The average total duration was statistically

different (P value < 0,001) between the OE group (295 ± 62,2 min) and the MIE group (363 ± 56,1 min). The same result was found for the data concerning the abdominal and thoracic phase durations, even if the number of patient considered was inferior*. The average duration of the abdominal phase was 158 ± 46,9 min for the OE group and 183 ± 40,6 min for the MIE group (P value < 0,006). The average duration of the thoracic phase was 162 ± 36,6 min for the OE group and 179 ± 30,5 min for the MIE group (P value < 0,018).

4.3. Pathological examination results

No statistical differences were found between the OE group and the MIE group analyzing the surgical radicality data (Tab. VII).

Table VII. Surgical Radicality.

VARIABLES	OE GROUP	MIE GROUP	P value
Radicality R0	136 (98,6%)	61 (100%)	ns
Positive proximal resection margin	1 (0,7%)	0 (0%)	ns
Positive distal resection margin	1 (0,7%)	0 (0%)	ns

Surgical radicality, according to the College of American Pathologists esophageal cancer protocol,[56] was achieved in a total number of 197 (99,0%) patients considering the distal and proximal margin involvement. 1 patient had a positive proximal resection margin. 1 patient had a positive distal resection margin.

Mean values for the number and tumor involvement of lymph nodes are summarized in Tab VIII.

Table VIII. lymph nodes analyses.

VARIABLES	OE GROUP*	MIE GROUP*	P value
Total lymph nodes	20,8 ± 9,6	27,4 ± 10,1	**<0,001**
Total lymph nodes positive	1,6 ± 3,0	1,5 ± 3,1	ns
Abdominal lymph nodes*	12,8 ± 7,5	16,7 ± 7,5	**<0,001**
Abdominal lymph nodes positive*	1,2 ± 2,5	1,0 ± 2,3	ns
Thoracic lymph nodes*	7,4 ± 5,0	10,4 ± 6,8	**<0,001**
Thoracic lymph nodes positive*	0,3 ± 0,1	0,2 ± 0,1	ns

**Data on abdominal and thoracic lymphadenectomy were missing in some pathology reports, reducing the numerosity of the OE group to 133 patients, and that of the MIE group to 58.*

The total number of lymph nodes harvested was statistically different between the OE and the MIE group, with an average value of 20,8 ± 9,6 for the OE group and 27,4 ± 10,1 for the MIE group (P value < 0,001). The same difference was found between the two groups for the number of abdominal and thoracic lymph nodes yielded (P value < 0,001). The average number of lymph node harvested during the abdominal phase was 12,8 ± 7,5 for the OE group and 16,7 ± 7,5 for the MIE group, while during the thoracic phase was 7,4 ± 5,0 for the OE group and 10,4 ± 6,8 for the MIE group. Tumor involvement of lymph nodes, on the other hand, showed no statistical differences between the two groups. The mean values of positive lymph nodes harvested were 1,6 ± 3,0 overall, 1,1 ± 2,4 considering only the abdominal lymph nodes and 0,3 ± 0,9 considering only the thoracic lymph nodes.

Regarding the pathological tumor stage, there were no statistical differences between the OE and MIE group, even when considering the Tumor, Lymph node, and Metastasis parameters of pTNM classification separately (Tab. IX).[17]

Table IX. pTNM classification.[17]

VARIABLES	OE GROUP	MIE GROUP	P value
pT			ns
0	31 (22,5%)	15 (24,6%)	
Tis	1 (0,7%)	0 (0%)	
T1a	10 (7,2%)	2 (3,3%)	
T1b	16 (11,6%)	6 (9,8%)	
T2	20 (14,5%)	16 (26,2%)	
T3	54 (39,1%)	21 (34,4%)	
T4a	5 (3,6%)	1 (1,6%)	
T4b	1 (0,7%)	0 (0%)	
pN			ns
N0	82 (59,4%)	36 (59,0%)	
N1	29 (21,0%)	13 (21,3%)	
N2	17 (12,3%)	7 (11,5%)	
N3	10 (7,2%)	5 (8,2%)	
pM			ns
M0	134 (97,1%)	61 (100%)	
M1	4 (2,9%)	0 (0%)	
Pathologic Stage			ns
0	31 (22,5%)	15 (24,6%)	
Ia	6 (4,3%)	2 (3,3%)	
Ib	14 (10,1%)	6 (9,8%)	
Ic	5 (3,6%)	1 (1,6%)	
IIa	6 (4,3%)	6 (9,8%)	
IIb	28 (20,3%)	6 (9,8%)	
IIIa	4 (2,9%)	8 (13,1%)	
IIIb	27 (19,6%)	12 (19,7%)	
IVa	14 (10,1%)	5 (8,2%)	
IVb	3 (2,2%)	0 (0%)	

4.4. Postoperative complications

There was no statistical significant difference between both the type and gravity of postoperative complications. The results of the comparisons between the two groups are summarized in Tab. X, Tab. XI and Tab. XII.

Table X. types of surgical complications

VARIABLES	OE GROUP	MIE GROUP	P value
Overall complications	75 (54,3%)	30 (49,2%)	ns
Infective complications	40 (29,0%)	21 (34,4%)	ns
Pulmonary complications	33 (23,9%)	11 (18,0%)	ns
Urologic complications	19 (13,8%)	8 (13,1%)	ns
Thromboembolic complications	10 (7,2%)	5 (8,2%)	ns
Neurologic/psychiatric complications*	10 (7,2%)	3 (4,9%)	ns
Cardiac complications	7 (5,1%)	5 (8,2%)	ns
Gastrointestinal complications*	8 (5,8%)	2 (3,3%)	ns
Wound/diaphragm complications	5 (3,6%)	2 (3,3%)	ns
Other complications*	3 (2,2%)	1 (1,6%)	ns

**Anastomotic leaks, chyle leaks, recurrent nerve injuries/palsis are analyzed separately.*

The overall complication rate was 52,8%. Listed below are the rates of each type of complication in order of prevalence:

- Infective complications - 30,7%
- Pulmonary complications - 22,1%
- Urologic complications - 13,6%
- Thromboembolic complications - 7,5%
- Neurologic/psychiatric complications - 6,5%
- Cardiac complications - 6,0%
- Gastrointestinal complications - 5,0%
- Wound/diaphragm complications - 3,5%
- Other complications - 2,0%

Considering anastomotic leaks, chyle leaks and recurrent nerve injuries/palsis in the prevalence count, the rate of gastrointestinal complications rises to 15,6%, the rates of neurologic/psychiatric complications increases reaching 10,1% and the rates of other complications becomes 3,5%.

Table XI. Anastomotic leaks, chyle leaks, recurrent nerve injuries/palsis

VARIABLES	OE GROUP	MIE GROUP	P value
Anastomotic leak	13 (9,4%)	8 (13,1%)	ns
Anastomotic leak type			ns
1	6 (4,3%)	3 (4,9%)	
2	6 (4,3%)	4 (6,6%)	
3	1 (0,7%)	1 (1,6%)	
Conduit necrosis	0 (0%)	0 (0%)	ns
Chyle leak	2 (1,4%)	1 (1,6%)	ns
Chyle leak type			ns
1	1 (0,7%)	0 (0%)	
2	0 (0%)	0 (0%)	
3	1 (0,7%)	1 (1,6%)	
Vocal Cord Injury/Palsy	7 (5,1%)	0 (0%)	ns

The rate of anastomotic leak was 10,6%, with no statistical significant differences between types. No conduit necrosis was recorded. The rate of chyle leak was 1,5%, with no statistical differences between types. The rate of vocal cord injury/palsy was 3,5% and all cases occurred in the OE group.

Table XII. Clavien Dindo classification of surgical complications severity.[64]

VARIABLES	OE GROUP	MIE GROUP	P value
CD most severe			ns
0	63 (45,7%)	31 (50,8%)	
1	9 (6,5%)	3 (4,9%)	
2	33 (23,9%)	11 (18,0%)	
3a	19 (13,8%)	9 (14,6%)	
3b	0 (0%)	1 (1,6%)	
4a	8 (6,0%)	4 (6,6%)	
4b	3 (2,2%)	2 (3,3%)	
5	3 (2,2%)	0 (0%)	
Severe complications			ns
CD 0-2	105 (76,1%)	45 (73,8%)	
CD 3-5	33 (23,9%)	16 (26,2%)	

No statistically significant differences were found in the severity of surgical complications between the OE group and the MIE group. The overall incidence of severe surgical complications (Clavien Dindo grade 3, 4 and 5) was 24,6%. 3 patients (2,2%) died due to surgical complications and all belonged to the OE group.

4.5. Postoperative course

The data concerning the postoperative course are recorded in Tab. XIII

Table XIII. Postoperative course.

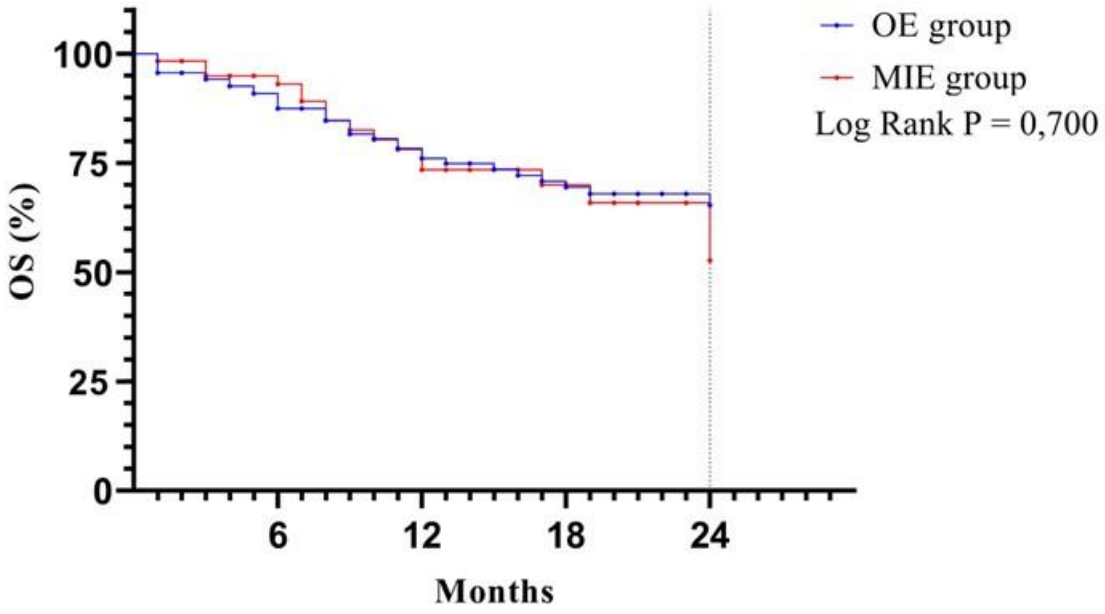
VARIABLES	OE GROUP	MIE GROUP	P value
Total blood transfusions (blood units)	0,7 ± 1,7	0,1 ± 0,3	**0,019**
Total ICU stay (days)	3 ± 8,3	1,1 ± 2,1	ns
Hospital stay (days)	15,6 ± 11,8	16 ± 15,0	ns
90-day readmission	9 (6,5%)	1 (1,6%)	ns
90-day mortality	5 (3,6%)	1 (1,6%)	ns

The average number of blood transfusions during the hospital stay was significantly lower in the MIE group, with an average of 0,7 ± 1,7 blood units for the OE group and 0,1 ± 0,3 blood units for the MIE group (P value = 0,019). The total time spent in the ICU was not significantly different in the two groups, but a trend toward shorter length of stay can be seen for patients who underwent Minimally Invasive Esophagectomy. The average ICU length of stay was 3 ± 8,3 days for the OE group and 1,1 ± 2,1 days for the MIE group. The average hospital length of stay was 15,6 ± 11,8 days for the OE group and 16 ± 15,0 days for the MIE group, with no statistical difference. The 90-day readmission rate was 5,0%, 9 patients from the OE group and 1 from the MIE group were readmitted during the considered period. The 90-day mortality rate was 3,0%, 5 patients from the OE group and 1 from the MIE group died during the considered period.

4.6. Follow-up

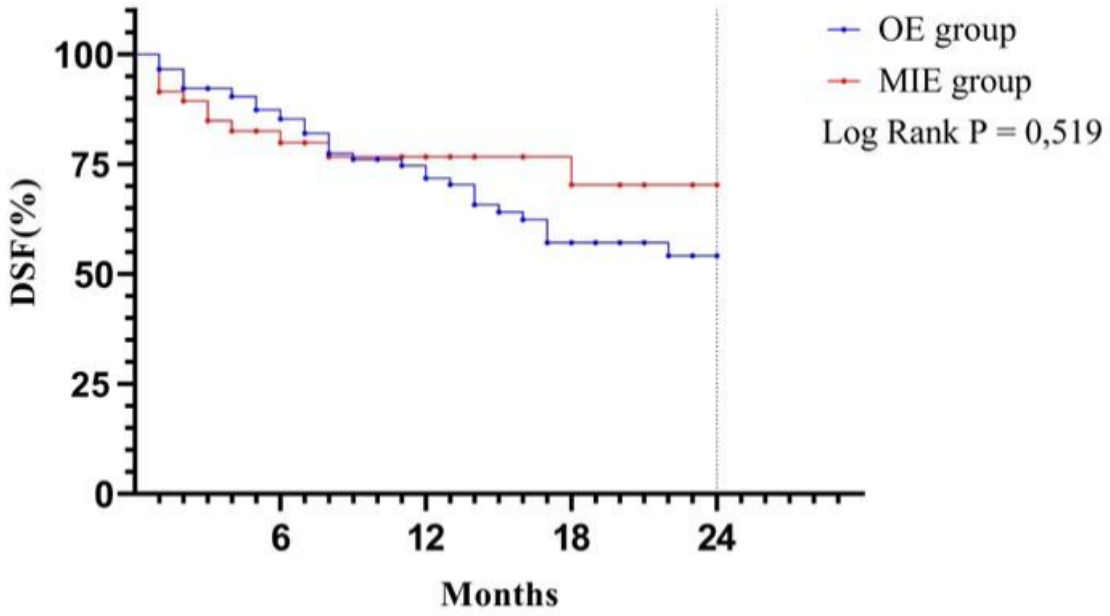
There were no statistical differences in Overall Survival (OS) and Disease-Free Survival (DSF) at 2 years between OE and MIE group (Fig. 22, Fig. 23). The median follow-up time was 12 months.

Figure 22. Kaplan-Meier estimate of overall survival.



Number at risk					
OE	138	106	68	51	26
MIE	61	50	34	19	10

Figure 22. Kaplan-Meier estimate of disease-free survival.



Number at risk					
OE*	118	84	52	31	15
MIE*	47	31	21	12	5

**The numerosity of OE and MIE groups is lower because there were some patients who presented with relapse and whose disease-free period is unknown.*

4.7. Comparison of early and late experience

To compare the Early Experience (EE) to the Late Experience (LE) of the center, the first 31 patients from the MIE group were assigned to the EE group and the last 30 to the LE group. The Early Experience period included the first 26 months of experience and the Late Experience group the last 26 months (the study period was 52 months in total). Preoperative characteristics of the two groups are summarized in Tab. XIV. No significant differences were found.

Table XIVa. patient's characteristics.
EE GROUP = Early Experience group
LE GROUP = Late Experience group

VARIABLES	EE GROUP	LE GROUP	P value
Sex			ns
male	27 (87,1%)	27 (90,0%)	
female	4 (12,9%)	3 (10,0%)	
Age (years)	61,7 ± 11,0	51,4 ± 10,3	ns
Charlson Comorbidity Index	4,5 ± 1,7	3,7 ± 1,5	ns
BMI (Kg/m^2)	24,8 ± 4,6	25 ± 4,0	ns
ASA grade			
1	1 (3,2%)	0 (0%)	
2	17 (54,8%)	22 (73,3%)	ns
3	13 (41,9%)	8 (26,7%)	
Tumor histology			ns
AC	24 (77,4%)	24 (80,0%)	
SCC	7 (22,6%)	6 (20,0%)	

Table XIVb. patient's characteristics.

VARIABLES	EE GROUP	LE GROUP	P value
Clinical stage			ns
1	1 (3,2%)	3 (10%)	
2	6 (19,4%)	3 (10%)	
3	24 (77,4%)	24 (80%)	
4	0 (0%)	0 (0%)	
Neoadjuvant therapy			ns
no	7 (22,6%)	4 (12,9%)	
CRT	15 (48,4%)	12 (40%)	
CT	9 (29,0%)	14 (46,7%)	
RT	0 (0%)	0 (0%)	

Tab. XV reports the surgical outcomes analyses of the EE and LE group.

Table XV. surgical outcomes analyses.

VARIABLES	EE GROUP	LE GROUP	P value
Anastomosis reinforcement	28 (90,3%)	19 (63,3%)	**0,012**
Conversion to open	5 (16,1%)	3 (10,0%)	ns
Diameter circular stapler (mm)			ns
25	29 (93,5%)	29 (96,7%)	
28	2 (6,5%)	1 (3,3%)	
Total duration (min)	358 ± 52,1	368 ± 60,5	ns
Abdominal duration (min)*	178 ± 36,7	190 ± 44,8	ns
Thoracic duration (min)*	175 ± 168	184 ± 180	ns

**The Abdominal Duration and Thoracic Duration fields consider only a portion of the patients enrolled in the study, 27 for the EE group and 22 for the LE group, respectively; data for the remaining patients were missing from the anesthesiology reports.*

The only statistical difference related to surgical outcomes between the two groups was in the rates of anastomosis reinforcement, with a preference to perform reinforcement more often in the EE group (90,3%) than in the LE group (63,3%), P value = 0,012. The fields conversion to open rate, diameter of circular stapler and operative duration didn't show any statistical significant difference.

Tab. XVI shows the pathologic examination results analyses.

Table XVIa. Pathologic examination results analyses.

VARIABLES	EE GROUP	LE GROUP	P value
Radicality R0	31 (100%)	30 (100%)	ns
Positive proximal resection margin	0 (0%)	0 (0%)	ns
Positive distal resection margin	0 (0%)	0 (0%)	ns
Total lymph nodes	26,7 ± 9,7	28,2 ± 10,5	ns
Total lymph nodes positive	2,7 ± 4,0	0,3 ± 0,6	**0,002**
Abdominal lymph nodes*	17,5 ± 7,0	15,9 ± 8,2	ns
Abdominal lymph nodes positive*	1,9 ± 2,9	0,1 ± 0,6	**0,002**
Thoracic lymph nodes*	9 ± 5,8	11,8 ± 7,5	ns
Thoracic lymph nodes positive*	0,3 ± 0,6	0,1 ± 0,3	ns

**Data on abdominal and thoracic lymphadenectomy were missing in some pathology reports, reducing the numerosity of the EE group to 30 patients, and that of the LE group to 28.*

Radicality was archived in all patients considering the distal and proximal margin involvement. The total number of positive lymph nodes harvested was superior in the EE group (2,7 ± 4,0) compared to the LE group (0,3 ± 0,6), P value = 0,002. The same result was found regarding the number of positive abdominal lymph nodes, with a higher number in the EE group (17,5 ± 7,0) compared to the LE group (0,1 ± 0,6), P value = 0,002. The number of thoracic lymph nodes was similar between the two groups.

Table XVb. Pathologic examination results analyses.

VARIABLES	EE GROUP	LE GROUP	P value
pT			ns
0	5 (16,1%)	0 (0%)	
Tis	0 (0%)	0 (0%)	
T1a	0 (0%)	2 (6,7%)	
T1b	2 (6,5%)	4 (13,3%)	
T2	9 (29,0%)	7 (23,3)	
T3	14 (45,2%)	7 (23,3)	
T4a	1 (3,2%)	0 (0%)	
T4b	0 (0%)	0 (0%)	
pN			**0,004**
N0	12 (38,7%)	24 (80%)	
N1	8 (25,8%)	5 (16,7%)	
N2	6 (19,4%)	1 (3,3%)	
N3	5 (16,1%)	0 (0%)	
pM			ns
M0	31 (100%)	30 (100%)	
M1	0 (0%)	0 (0%)	
Pathologic stage			ns
0	5 (16,1%)	10 (33,3%)	
Ia	0 (0%)	2 (6,7%)	
Ib	2 (6,5%)	4 (13,3%)	
Ic	0 (0%)	1 (3,3%)	
IIa	2 (6,5%)	4 (13,3%)	
IIb	3 (9,7%)	3 (10,0%)	
IIIa	6 (19,4%)	2 (6,7%)	
IIIb	8 (25,8%)	4 (13,3%)	
IVa	5 (16,1%)	0 (0%)	
IVb	0 (0%)	0 (0%)	

The pN parameter showed a statistically significant difference between the EE group and the LE group (P value = 0,004), as expected considering the surgical outcomes.

Postoperative complications rates are summarized in Tab. XVI.

Table XVI. Postoperative complications analyses.

VARIABLES	EE GROUP	LE GROUP	P value
Overall complications	19 (61,3%)	11 (36,7%)	ns
Infective complications	17 (54,8%)	4 (13,3%)	**<0,001**
Pulmonary complications	7 (22,6%)	4 (13,3%)	ns
Urologic complications	4 (12,9%)	4 (13,3%)	ns
Thromboembolic complications	5 (16,1%)	0 (0%)	**0,022**
Neurologic/psychiatric complications	3 (9,7%)	0 (0%)	ns
Cardiac complications	4 (12,9%)	1 (3,3%)	ns
Gastrointestinal complications*	1 (3,2%)	1 (3,3%)	ns
Wound/diaphragm complications	1 (3,2%)	1 (3,3%)	ns
Other complications	0 (0%)	1 (3,3%)	ns
Anastomotic leak*	5 (16,1%)	3 (10,0%)	ns
Anastomotic leak type			ns
1	2 (6,5%)	1 (3,3%)	
2	2 (6,5%)	2 (6,7%)	
3	1 (3,2%)	0 (0%)	
Conduit necrosis	0 (0%)	0 (0%)	ns
Chyle leak	0 (0%)	0 (0%)	ns
Vocal Cord Injury/Palsy	0 (0%)	0 (0%)	ns

**Anastomotic leaks are analyzed separately from the gastrointestinal complications.*

Overall there wasn't a statistically significant difference in the occurrence of postoperative complications in the two groups, but a tendency can be seen towards a reduction of the incidence in the LE group (36,7%) compared to the EE group (61,3%). There was a significant difference in the incidence of infective complications, 13,3% in the LE group compared to 17% in the EE group (P value < 0,001). There was also a significant difference in the incidence of thromboembolic complications, none in the LE group compared to 16,1% in the EE group (P value = 0,022).

Tab. XVII summarized the analyses regarding the severity of surgical complications. No statistically significant differences were found.

Table XVII. postoperative complications severity analyses.

VARIABLES	EE GROUP	LE GROUP	P value
CD most severe			ns
0	12 (38,7%)	19 (63,3%)	
1	2 (6,5%)	1 (3,3%)	
2	6 (19,4%)	5 (16,7%)	
3a	6 (19,4%)	3 (10,0%)	
3b	0 (0%)	1 (3,3%)	
4a	3 (9,7%)	1 (3,3%)	
4b	2 (6,5%)	0 (0%)	
5	0 (0%)	0 (0%)	
Severe complications			ns
CD 0-2	20 (64,5%)	25 (83,3%)	
CD 3-5	11 (35,5%)	5 (16,7%)	

Tab. XVIII shows the results concerning the postoperative course of the patients.

Table XVIII postoperative course results.

VARIABLES	EE GROUP	LE GROUP	P value
Total blood transfusions (blood units)	0,2 ± 0,5	0 (0%)	ns
Total ICU stay (days)	1,6 ± 2,4	0,6 ± 1,5	**0,049**
Hospital stay (days)	19,6 ± 19,8	12,2 ± 5,9	ns
90-day readmission	1 (3,2%)	0 (0%)	ns
90-day mortality	0 (0%)	1 (3,3%)	ns

The total number of blood transfusions wasn't statistically different between groups, but the only blood units administered were in the EE group. The only statistically significant difference found in the postoperative parameters concerned the total ICU stay (calculated as the total number of days spent in the ICU during hospitalization). The mean value was 1.6 ± 2.4 days for the EE group and 0.6 ± 1.5 days for the LE group (P value = 0.049). In the LE group compared with the EE group, there was also a trend toward a shorter hospital stay.

4.8. Learning curves

Fig. 23 and Fig. 24 show the learning curve impact associated with the total ICU stay and Hospital stay. On visual analysis, a decrease in total ICU stay can be seen starting with patient number 25. The same is true for hospital stay, although there is no statistical difference between the EE and LE group.

Figure 23. Cumulative sum (CUSUM) plot for total ICU stay

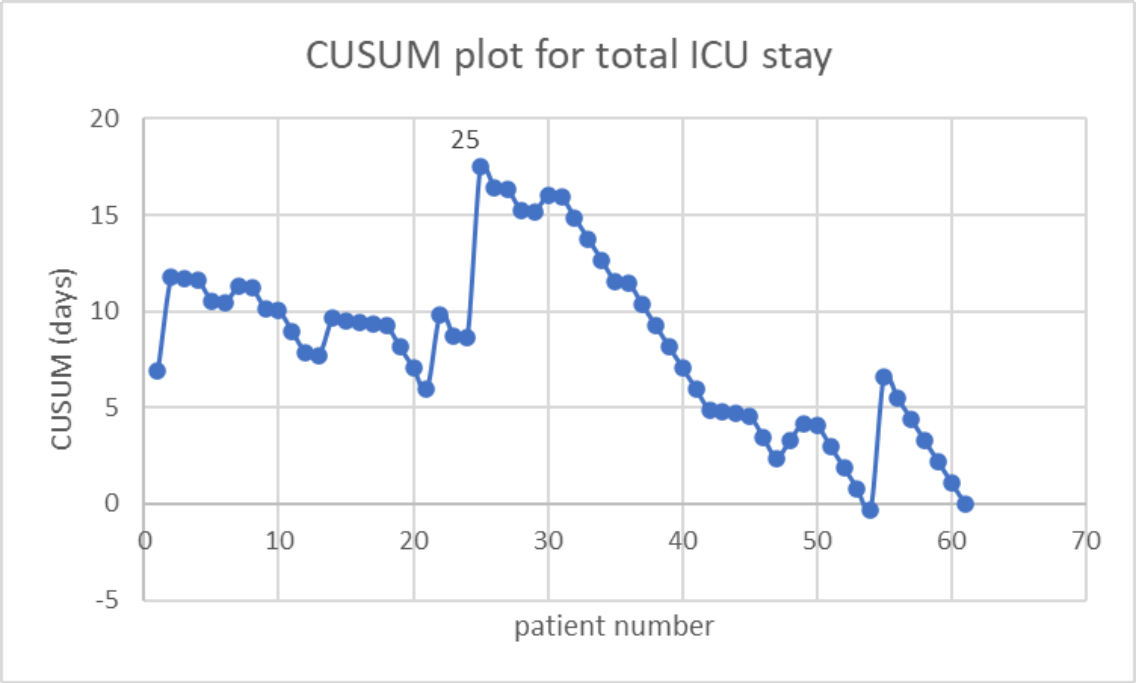
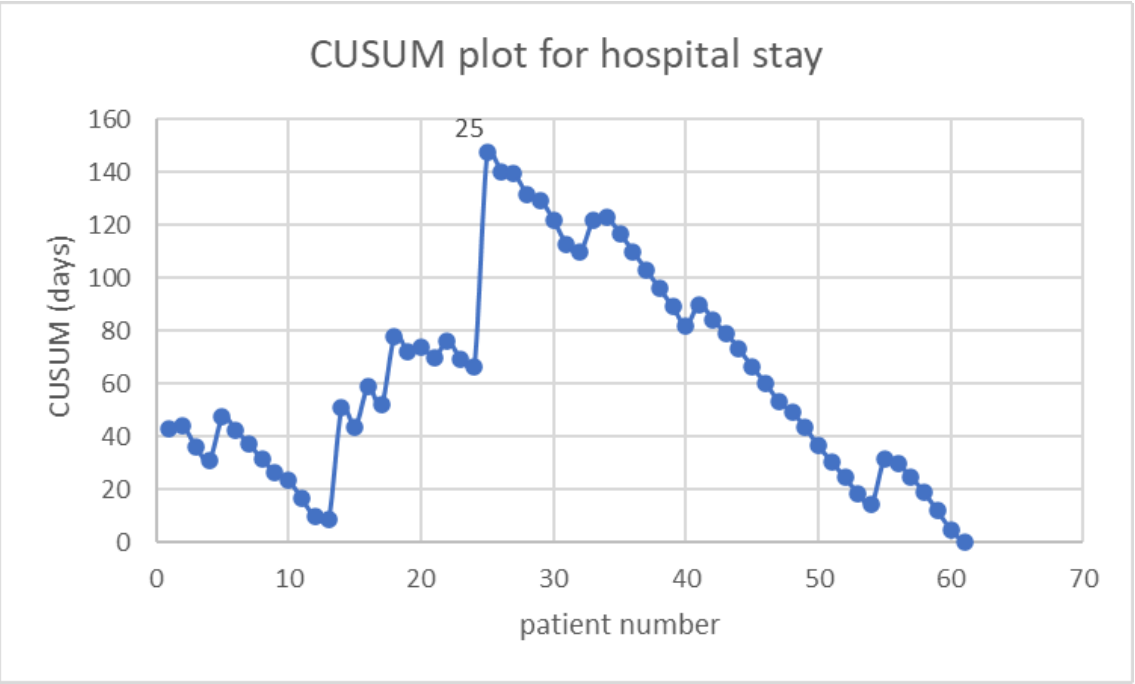


Figure 24. Cumulative sum (CUSUM) plot for hospital stay.



5. DISCUSSION

The Minimally Invasive Ivor Lewis Esophagectomy is a technically difficult procedure that calls for advanced thoracoscopic and laparoscopic skills. With practice, the procedure can be successfully performed both in terms of perioperative morbidity and oncologic efficacy.[45-51] When interpreting outcome data collected during an implementation period, however, it's crucial to take surgical learning curves into consideration. The aim of this study is to evaluate the safety and efficacy of implementing a totally minimally invasive esophagectomy program in our high-volume Upper GI Surgery Unit.

5.1. Results of the program implementation

Preoperative characteristics of the study population are similar between the OE and MIE group when considering sex, BMI, ASA grade, tumor histology, clinical stage, and administration of neoadjuvant therapy. The groups differed in age and Charlson comorbidity index (CCI); patients were slightly younger and healthier in the MIE group than in the OE group. The mean age was 60,1 ± 10,7 years versus 63,8 ± 11,1 years (P value 0,030), and the mean CCI was 4,1 ± 1,6 points versus 4,9 ± 1,90 points (P value 0,005) in the MIE group compared with the OE group. This finding could be explained by the tendency, especially in early experience, to select patients with fewer comorbidities for the minimally invasive approach. However, patients with a comorbidity index greater than seven are present in both categories, proving that high comorbidity rates are not a contraindication to performing MI-ILE.

Surgical outcomes analisis show an evident preference to perform anastomosis reinforcement in the MIE group compared to the OE group (77,0% vs 17,4%, P value < 0,001), this finding may be explained by the intention to reduce the rate of reintervention associated with MI-ILE that some studies suggest.[48,49] Another significant trend that can be seen in the MIE group compared with the OE group concerns the smaller diameter of the circular stapler used during surgery. There is a preference in using the 25-mm diameter circular stapler (95,1%) in comparison with the OE group (50,7%). Total duration of surgery was significantly longer in the MIE group compared

to the OE group (363 ± 56,1 vs 295 ± 62,2 - P value < 0,001) as expected and widely report in literature.[47,48,49] The same results were found analyzing the abdominal duration (183 ± 40,6 vs 158 ± 46,9, P value < 0,001) and thoracic duration (179 ± 30,5 vs 162 ± 36,6, P value < 0,001).

Pathological examination results analisis show an uncompromised ability to perform radical resections between the two approaches. The fact that in open surgery we perform more complex and extended resections for advanced tumors may account for the two patients in the OE group who presented the proximal and distal margin involved by tumor infiltration. The literature's findings on the quality of the lymphadenectomy are still debatable; some studies report a similar or noticeably higher number of lymph nodes removed during MIE than during OE,[65,66,67] while other studies report a less successful lymph node yield during MIE.[68,69,70] Our study shows a statistically significant difference in lymph nodes harvesting, with an average of 20,8 ± 9,6 lymph nodes in the OE and 27,4 ± 10,1 in the MIE group (P value < 0,001). The superiority of the minimally invasive approach could be explained by the magnified visualization permitted by this technique, which translates in a more complete lymphadenectomy.[42] The same results were found for the number of lymph nodes harvested in the abdominal and thoracic phases, although the number of patients considered for this analysis was not complete due to the lack of information in the pathology reports. The average number of lymph nodes extracted during the abdominal phase was 16,7 ± 7,5 for the MIE group and 12,8 ± 7,5 for the OE group. The average number of lymph nodes extracted during the abdominal phase was 10,4 ± 6,8 for the MIE group and 7,4 ± 5,0 for the OE group. The number of positive lymph nodes yielded wasn't statistically different between the two approaches. No statistically significant differences were found between the groups of the pathological stage either.

Between the OE group and the MIE group, there were no significant differences in the incidence of postoperative complications. There was no difference between the groups even after taking the Clavien-Dindo scale into account for severity stratification. One of the most frequently mentioned advantages of MIE in the literature is a decrease in pulmonary morbidity because a thoracotomy incision is avoided.[67] According to TIME trial[47], the rate of pulmonary infections of MIE compare to the one of OE significantly decreased (29% vs. 57%). A recent meta-analysis found that the rate of pulmonary

complications decreased from 22,6% in OE to 17,1% in MIE.[66] Since few studies actually define respiratory complications it is challenging to compare the related outcomes. We did not find a statistically significant difference between the two groups in our series. Anastomotic leak rates in minimally invasive esophagectomies vary widely in the literature (especially when different techniques are taken into account), but there is no evidence that anastomosis leak rates are lower in the minimally invasive compared to open approach.[47-51] In our experience, there was no significant difference between the MIE and OE group when it came to anastomotic leaks requiring medical or surgical treatment. None of the patients was affected by conduit necrosis.

Postoperative course data analyses found no differences in hospital stay, total ICU stay, 90-day readmission and 90-day mortality. The lack of statistically significant difference in total ICU stay (calculated as total number of days spent in the ICU during hospitalization) between the two groups could be interesting, considering that the patients who underwent MIE were preferentially assisted in post-anesthesia care unit (PACU) immediately after surgery, compared to patients operated with the open approach. Furthermore, there are several studies that report shorter ICU length of stay and need for ventilation in patients who underwent MIE.[48,50] Considering the total number of blood transfusion there was a statistically significant difference between the two approaches, with an average need of 0,1 ± 0,3 blood units for the patients of the MIE group and 0,7 ± 1,7 blood units for the patients of the OE group (P value = 0,019). This outcome was expected considering that this evidence is widely reported in literature.[47-51]

5.2. Early vs late experience

According to several studies, learning a technically difficult procedure like Minimally Invasive Ivor Lewis Esophagectomy can take years, and results can be seriously affected during the learning phase.[44,71,72] In addition, high-volume centers appear to have shorter learning curves than low-volume centers.[74]

All surgical resections performed were radical: there was no proximal or distal margin involvement, demonstrating that lack of experience did not compromise surgical radicality. The lymph nodes number was not impaired in the early experience compared

with the late experience, but there was an unexpected increase in positive abdominal lymph nodes (which resulted in a higher number of total positive lymph nodes): a mean value of 1,9 ± 2,9 positive abdominal lymph nodes was found in the EE group and 0,1 ± 0,6 positive abdominal lymph nodes in the LE group. We believe that this result may be due to the small sample size considered.

There was no statistically significant difference in overall complication rates between early and late experience, although a trend toward decreasing complication rates can be seen in the late phase of the program implementation. This finding is supported by the significant decrease of infective and thromboembolic complications rates: infective complications rate decreased from 54,8% to 13,3% (P value < 0,001), thromboembolic complications rate decreased from 16,1% to 0% (P value 0,022). A considerable learning curve impact was discovered in several studies to affect the postoperative course and complication rate. For example, in the experience of van Workum et al.[73], anastomotic leakage decreased from 18,9% to below 5% with a mean of 119 cases before plateauing. The majority of investigations revealed that throughout the learning curve period, anastomotic leakage decreased by at least 10%.[71] Although we did not find significant differences in anastomotic leakage rates, we believe our results may suggest an impact of the learning curve on postoperative morbidity rates.

The only statistical significative difference found in the postoperative parameters considered involved the total ICU stay, with a decrease in the late experience group (mean value of 0,6 ± 1,5 days) compared to the early experience group (mean value of 1,6 ± 2,4 days), P value 0,049. A decreasing trend was also observed in hospital stay and the need for blood transfusions, with no statistically significant differences between the two groups. The surgical team may have grown more used to postoperative care as it gained experience with minimally invasive esophagectomy, which might account for the smoother and quicker recovery seen in the late experience group. Furthermore, from the analysis of the CUSUM plots of the total ICU and hospital stay, we suggest that about 25 patients are required to significantly improve postoperative management and care. 90-days mortality and 90-days readmission were similar between the two groups. Comparing our results with data available in the literature,[71,72,74] we observed that the duration of the learning curve in our center is shorter than that of most centers, so we suggest that the implementation of a totally minimally invasive esophagectomy program

in a high-volume center with decades of experience in treating esophageal cancer could reduce the rates of postoperative complications and recovery associated with learning more rapidly than in centers with lower experience and patient volumes.

5.3. Study limits and prospects

The study's design has both advantages and disadvantages. Despite not being randomized and being prospective, the study still allows for an accurate representation of surgical outcomes. The choice of treatment modality is subject to bias, particularly the preference of the surgeon for the surgical method. In our center, the choice of an open approach is still influenced by tumor characteristics (especially in the early experience), which may bias against similar outcomes between patients chosen for MIE vs. OE. Even though we showed that there is no statistical difference between the two groups' pathological tumor staging following surgery, locally advanced tumors or the anticipated need for complex end extended resection still rule out a minimally invasive approach. A further drawback of this study may be the relatively small proportion of included patients who underwent Minimally Invasive Ivor Lewis Esophagectomy in comparison to other studies. However, the majority of studies in literature analyzed all three minimally invasive approaches equally and over extended time periods, which produced a chronological bias: it is unlikely that the surgical method and management strategy employed over such a long period of time remained uniform. To report on the oncological results of this series, more research and longer follow-up will be required. Finally, to maintain and enhance elevated surgical outcomes, future development of this minimally invasive esophagectomy program should incorporate the implementation of an improved recovery protocol.

6. CONCLUSIONS

The findings of this study support the safety and efficacy of implementing a totally minimally invasive esophagectomy program for cancer in a high-volume center. In comparison to open technique, surgical and oncological outcomes, postoperative complication rates, morbidity and mortality rates were not compromised by the learning curve effect and met current international standards. According to our observations, MIE results in higher rates of lymph node yield, both in the abdominal and thoracic field. We therefore propose that the effect of laparoscopic magnification can aid in a more accurate and precise lymph node dissection. Additionally, patients who underwent minimally invasive surgery required fewer blood transfusions while they were hospitalized. Comparing the outcomes of the early experience with those of the late experience, we discovered improving trends in postoperative complication and recovery rates. In our high-volume center's experience, improving these outcomes has required 25 to 30 cases.

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