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DISSERTATION

Introduction of hybrid minimally invasive esophagectomy and comparison of perioperative outcomes following open versus hybrid esophagectomy; a propensity-matched retrospective study.

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Contents

Abbrevations

AC	Adenocarcinoma
ARDS	Acute Respiratory Distress Syndrome
AJCC	American Joint Committee on Cancer
BE	Barrett's Esophagus
BMI	Body Mass Index
CRP	C-Reactive Protein
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CI	Confidence Interval
DGE	Delayed Gastric Emptying
EU	Endoscopic Ultrasound
EUS-FNA	Endosonographic-directed Fine-Needle Aspiration
EC	Esophageal cancer
ECCG	Esophageal Complications Consensus Group
EGD	Esophagogastroduodenoscopy
GERD	Gastroesophageal Reflux Disease
GEJ	Gastroesophageal Junction
Hb	Hemoglobin
HMIE	Hybrid Minimally Invasive Esophagectomy
ICU	Intensive Care Unit
IQR	Interquartile Ranges
IMCU	Intermediate Care Unit
LN	Lymph Node/s
MIE	Minimally Invasive Esophagectomy
MODS	Multiple Organ Dysfunction Syndrome

NCCN	National Comprehensive Cancer Network
OSAS	Obstructive Sleep Apnea Syndrome
OE	Open Esophagectomy
OR	Odds Ratio
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computed Tomography
RCT	Randomized Controlled Trial
SCC	Squamous Cell Carcinoma
TMIE	Total Minimally Invasive Esophagectomy
TNM	Tumor/Node/Metastasis
cTNM	clinical Tumor/Node/Metastasis
pTNM	pathological Tumor/Node/Metastasis
ypTNM	Postneoadjuvant Tumor/Node/Metastasis
VAC	Vacuum Assisted Closure therapy
WBC	White Blood Cells

1 Summary

1.1 Abstract

INTRODUCTION: Esophagectomy is associated with increased rate of postoperative complications, making it one of the procedures with the highest impact on patients' quality of life. Hybrid Ivor Lewis esophagectomy with laparoscopy and thoracotomy has been developed with the aim to reduce postoperative morbidity without to compromise oncological outcomes. We conducted this survey under the hypothesis that the hybrid approach results in reduced postoperative complications with equivalent oncological outcomes in two similarly matched groups of patients.

METHODS: Propensity score matching was used to remove bias attributed to observational studies. After generating propensity scores using the variables age, body mass index, pulmonary comorbidities, cardiac comorbidities, histologic type, and neoadjuvant treatment, 17 patients in the hybrid group were matched with 17 patients in the open group. Surgical outcomes, oncological outcomes, and postoperative complications according to the guidelines of the Esophageal Complications Consensus Group were compared between the two groups.

RESULTS: Open and hybrid procedures showed similar surgical and oncological outcomes. Although the hybrid group spent more time in the intensive care unit, the length of hospital stay was comparable between the groups. The rate of postoperative complications was similar between the two approaches.

DISCUSSION: Our hypothesis that laparoscopy could reduce postoperative complications was not confirmed. Hybrid Ivor Lewis esophagectomy is a safe procedure, resulting in radical oncological resection and similar morbidity with open esophagectomy. Surgeons who are proficient in open approach and laparoscopic anti-reflux and gastric surgery can safely adopt the hybrid approach without significant learning curve associated morbidity.

1.2 Zusammenfassung

EINLEITUNG: Die Ösophagektomie ist mit einer erhöhten Rate postoperativer Komplikationen verbunden. Die hybride Ivor Lewis-Ösophagektomie mit Laparoskopie und Thorakotomie wurde mit dem Ziel entwickelt, die postoperative Morbidität zu reduzieren, ohne die onkologischen Ergebnisse zu beeinträchtigen. Wir haben diese Studie unter der Hypothese durchgeführt, dass der Hybridansatz bei zwei ähnlich übereinstimmenden Patientengruppen zu reduzierten postoperativen Komplikationen mit äquivalenten onkologischen Ergebnissen führt.

METHODEN: Es wurde propensity score matching angewandt, um Verzerrungen zu vermeiden, die prospektive Studien zugeschrieben werden. Nach der Erstellung von propensity scores unter Verwendung der Variablen Alter, Body-Mass-Index, Lungenkomorbiditäten, Herzkomorbiditäten, histologischer Typ und neoadjuvante Behandlung wurden 17 Patienten in der Hybridgruppe mit 17 Patienten in der offenen Gruppe verglichen. Chirurgische und onkologische Ergebnisse sowie postoperative Komplikationen wurden gemäß den Richtlinien von Esophageal Complications Consensus Group zwischen den beiden Gruppen verglichen.

ERGEBNISSE: Offene und hybride Verfahren zeigten ähnliche chirurgische und onkologische Ergebnisse. Obwohl die Patienten der Hybridgruppe längere Zeit auf der Intensivstation verbrachte, war die Dauer des Krankenhausaufenthalts zwischen den Gruppen wieder vergleichbar. Die Rate der postoperativen Komplikationen war zwischen den beiden Ansätzen ähnlich.

DISKUSSION: Unsere Hypothese, dass die Laparoskopie postoperative Komplikationen reduzieren könnte, wurde zumindest in der Phase der Einführung nicht bestätigt. Die hybride Ivor Lewis-Ösophagektomie erwies sich jedoch als ein sicheres Verfahren, das zu einer vergleichbaren radikalen onkologischen Resektion und einer ähnlichen Morbidität wie bei offener Ösophagektomie führt. Chirurgen, die mit offener Ösophagektomie und laparoskopischer Anti-Reflux- und Magenchirurgie Erfahrung haben, sind in der Lage das hybride Verfahren ohne signifikante Lernkurven-assoziierte Morbidität sicher anzuwenden.

2 Introduction

2.1 Epidemiology

Esophageal cancer (EC) is the ninth most common cause of cancer worldwide and the sixth leading cause of cancer-related deaths. In 2018 over 550,000 new cases of EC and 508,000 deaths related to EC were reported worldwide (BRAY et al., 2018). EC is more common in advanced age and is observed more commonly during the sixth and seventh decade of life. Median age of diagnosis is 68 years. Increased incidence of EC is reported in males. Specifically, 2-fold to 3-fold difference in incidence and mortality rates is reported between genders worldwide.

Incidence rates are variable worldwide, with highest rates reported in southern and eastern Africa and eastern Asia. In 2018, the highest incidence of EC was 24.7% in eastern Asia, whereas in western Europe and northern America was 8.5% and 6.8%, respectively (BRAY et al., 2018). Although many types of cancer are expected to decrease in incidence the next decades, the prevalence of EC is expected to increase by 140% (LAMBERT, HAINAUT, 2007). Epidemiologic factors such as gastroesophageal reflux disease, obesity, and Barrett's esophagus (BE) are thought to be related to the increased incidence of EC (PENNATHUR, LUKETICH, 2008).

2.2 Anatomy of Esophagus and Stomach

Esophagus lies between hypopharynx and stomach and is divided into cervical, thoracic, and abdominal esophagus. Cervical esophagus extends from cricopharyngeus to sternal notch and thoracic esophagus from sternal notch to esophageal hiatus. Thoracic esophagus is further divided into upper, middle, and lower esophagus (Figure 1). The abdominal part of esophagus, which is extended from esophageal hiatus to gastroesophageal junction (GEJ), is named abdominal esophagus.

The definition of the GEJ remains controversial. The GEJ has been defined histologically as the distal end of the submucosal esophageal glands or the proximal limit of the gastric oxyntic glands. Endoscopically, the squamocolumnar junction, or Z-line, and the proximal extent of the gastric mucosal folds define the GEJ .

The anatomy of stomach is crucial for the esophageal resection. Stomach is divided in five anatomic sections: cardia, fundus, body, pyloric antrum, and pylorus. The greater curvature of the stomach runs from the fundus along the left border of the body of the stomach and the inferior border of the pylorus. The lesser curvature starts at the right of the cardia and runs along the right border of the body of the stomach and the superior border of the pylorus.

The lesser curvature of the stomach is supplied by the right and left gastric artery. The greater curvature is supplied by the right and left gastroepiploic artery. The fundus of the stomach the upper portion of the greater curvature are supplied by the short gastric arteries, which arise from the splenic artery.

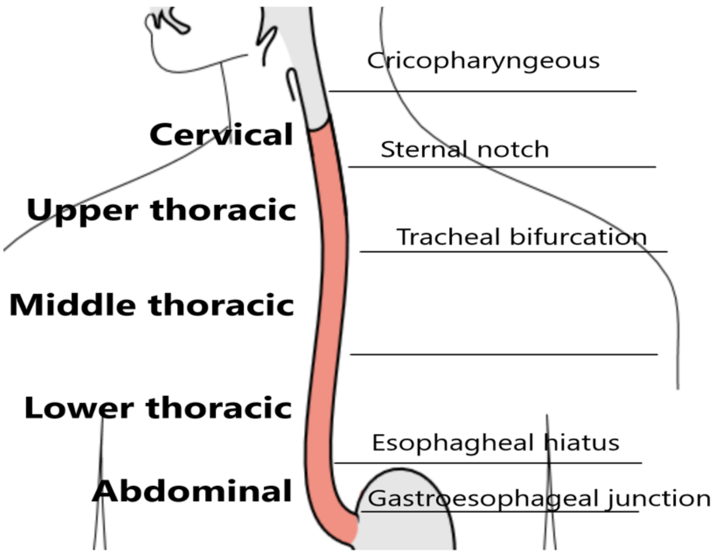

Figure 1: Anatomical regions of esophagus. Upper thoracic esophagus extends from sternal notch to tracheal bifurcation. The two equal portions between tracheal bifurcation and esophageal hiatus comprise the middle and lower thoracic esophagus.

2.3 Histological Types and Etiology of Esophageal Cancer

Until the 1970s, squamous cell carcinoma (SCC) had been detected in more than 90% of patients with EC in the United States. However, during the last years, the incidence of adenocarcinoma (AC) has been increased, representing the leading cause of EC in the USA and western Europe. It is estimated that approximately 90% of cases are AC, making this type of EC the fastest-growing cancer in the USA. However, SCC is the most common histological type of EC worldwide (LEPAGE et al., 2008). In China, it is estimated that more than 90% of patients with EC have SCC. Sarcomas and small cell carcinomas represent rare types of EC with incidence less than 2% (YANG et al., 2018).

The incidence of SCC is three times higher in blacks compared to whites. SCC can be developed in any part of esophagus since squamous cells line the entire epithelium of the organ. Alcohol consumption and tobacco use are risk factors for the development of SCC. Specifically, alcohol damages the cellular DNA by decreasing the metabolic activity within the cells; therefore, detoxification is inhibited, and oxidation is promoted (NAPIER et al., 2014). Also, alcohol is a solvent of fat-soluble compounds, allowing carcinogens within tobacco to penetrate the esophageal epithelium. Other carcinogens such as nitrosamines, which are found in salted vegetables and preserved fish, have been implicated in the development of SCC. Pathogenesis includes the inflammatory response of the squamous epithelium that leads to dysplasia and malignant transformation (MAO et al., 2011).

AC occurs in distal esophagus in 75% of the cases. Gastroesophageal reflux disease (GERD) is the most common risk factor for the development of AC (ZHANG, 2013). Prolonged exposure to the refluxate of GERD erodes the esophageal mucosa, promoting the replacement of healthy epithelium with metaplastic cells. AC represents the last event of a sequence that starts with GERD and progresses to Barrett metaplasia, low-grade, high-grade dysplasia, and finally, to AC (Figure 2).

The prevalence of BE, where the stratified squamous epithelium is replaced by columnar epithelium, is estimated at 2% in adult population. The majority of patients will not develop EC. However, the risk of AC in those patients is 50-100 times higher compared to healthy population (MAO et al., 2011). The risk of progression to AC is estimated around 0.5% annually in patients without dysplasia (HVID-JENSEN et al., 2011). Studies showed that more than 30% of patients with low-grade dysplasia will develop AC within five years (WANG et al., 2008). Progression of Barrett metaplasia to AC is related to mutations in gene structure, gene expression, and protein development. As potential markers are considered the oncosuppressor gene TP53 and the oncogene erb-52. Mutations in TP53 gene in patients with BE is associated with increased risk for AC (KOPPERT et al., 2005).

Obesity is another risk factor for AC. Individuals with increased body mass index (BMI) have 7.6-fold higher risk for EC (LAUBY-SECRETAN et al., 2016). Hypertrophied adipocytes and inflammatory reaction within fat deposits promote tumour development through release of adipokines and cytokines. In addition, adipocytes provide energy and support tumor development and progression. Finally, obesity increases the risk for GERD through increased intraabdominal and intragastric pressure, disruption of esophageal sphincter function, and increased risk of hiatal hernia (NIEMAN et al., 2013).

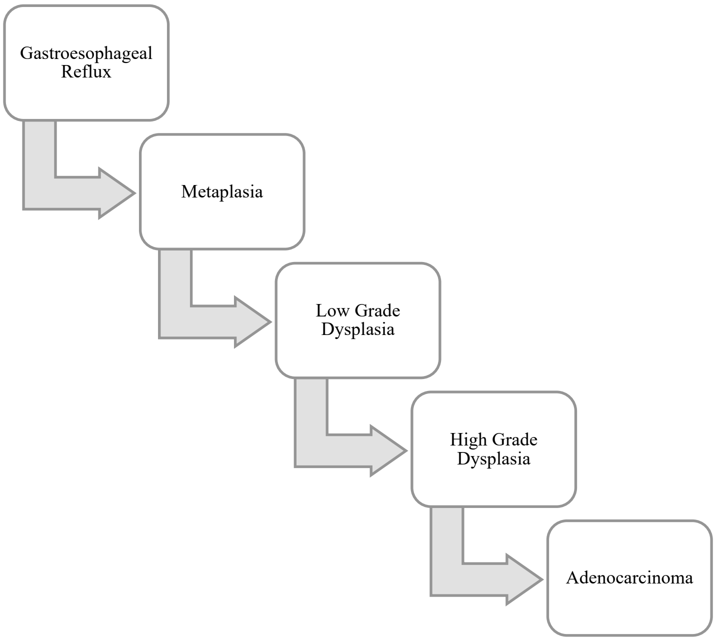

Figure 2: Cascade of events that leads from GERD to AC.

2.4 TNM Classification for Esophageal Cancer

The American Joint Committee on Cancer (AJCC) has developed a Tumor/Node/Metastasis (TNM) classification system for EC and GEJ cancer. Staging of EC includes the clinical (cTNM), pathological (pTNM), and postneoadjuvant (ypTNM) classification (RICE et al., 2017).

Clinical staging is based on the results of imaging examinations and histopathological analyses of biopsies. This classification is fundamental for the development of a management protocol.. Pathologic staging after surgical resection facilitates decision-making in post-esophagectomy period and constitutes the most accurate method to evaluate prognosis. pTNM classification, according to the 8th edition of AJCC, is demonstrated in Table 1 and 2. The 8th edition of AJCC, which was published in 2016, has introduced the postneoadjuvant staging for patients who underwent neoadjuvant treatment. The role of postneoadjuvant staging is limited in treatment planning. In case of AC with residual nodal disease, adjuvant chemotherapy can be performed. Postneoadjuvant classification is demonstrated in Table 3.

Table 1: Pathological stage groups (pTNM) for SCC according to the 8th edition of AJCC.

Pathologic (pTNM) Stage groups					
p Stage group	**pT**	**pN**	**pM**	**pGrade**	**pLocation**
Squamous cell carcinoma					
0	Tis	N0	M0	N/A	Any
IA	T1a	N0	M0	G1, X	Any

IB	T1b	N0	M0	G1-3, X	Any
	T1a	N0	M0	G2-3	Any
	T2	N0	M0	G1	Any
IIA	T2	N0	M0	G2-3, X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
IIB	T3	N0	M0	G2-3	Upper/middle
	T3	N0	M0	GX	Any
	T3	N0	M0	Any	X
	T1	N1	M0	Any	Any
IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
IIIB	T4a	N0-1	M0	Any	Any
	T3	N1	M0	Any	Any
	T2-3	N2	M0	Any	Any
IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	T1-4	N3	M0	Any	Any
IVB	T1-4	N0-3	M1	Any	Any

Table 2: Pathologic stage groups (pTNM) for AC according to the 8th edition of AJCC.

Adenocarcinoma					
0	Tis	N0	M0	N/A	
IA	T1a	N0	M0	G1, X	
IB	T1a	N0	M0	G2	
	T1b	N0	M0	G1-2, X	
IC	T1	N0	M0	G3	
	T2	N0	M0	G1-2	
IIA	T2	N0	M0	G3, X	
IIB	T1	N1	M0	Any	
	T3	N0	M0	Any	
IIIA	T1	N2	M0	Any	
	T2	N1	M0	Any	
IIIB	T4a	N0-1	M0	Any	
	T3	N1	M0	Any	
	T2-3	N2	M0	Any	
IVA	T4a	N2	M0	Any	
	T4b	N0-2	M0	Any	
	T1-4	N3	M0	Any	

	T1-4	N0-3	M1	Any	

(N/A, not applicable; X, not defined)

Table 3: Postneoadjuvant classification (ypTNM) for SCC and AC according to the 8th edition of AJCC.

Postneoadjuvant ypTNM Stage groups			
yp Stage group	**ypT**	**ypN**	**ypM**
I	T0-2	N0	M0
II	T3	N0	M0
IIIA	T0-2	N1	M0
IIIB	T4a	N0	M0
	T3	N1	M0
	T0-3	N2	M0
IVA	T4a	N1-2, X	M0
	T4b	N0-2	M0
	T1-4	N3	M0
IVB	T1-4	N0-3	M1

(X = not defined)

2.5 Neoadjuvant Therapy

The role of neoadjuvant chemoradiotherapy in the treatment of EC is fundamental. The majority of patients with resectable EC are presented with locally advanced disease. In this case, primary surgical resection is associated with poor survival. Neoadjuvant therapy provides several advantages in treatment of EC by downstaging cancer, eradicating micrometastases, decreasing cancer-cell dissemination during surgery, and increasing resectability. Additionally, neoadjuvant therapy is associated with reduced local and systemic recurrence and increased survival rates. Increased rates of postoperative complications or mortality are not reported in neoadjuvant treated patients (YANG et al., 2018).

Different neoadjuvant therapeutic options have been described, where chemotherapy and radiation are combined in the treatment of EC. Decrease in tumor size is achieved with radiation, whereas micrometastases and metastases outside the radiation field can be reached with chemotherapy. Recent evidence suggests that neoadjuvant chemoradiation followed by esophagectomy is the optimal approach for T3-4 tumors or nodal disease. Treatment of T2N0M0 tumors is controversial since studies, which evaluated the role of neoadjuvant therapy in this subgroup of patients, are limited. The German S3 guidelines recommend neoadjuvant chemoradiotherapy in patients with T2N0 AC or SCC.

The CROSS trial defined a new treatment protocol for patients with clinical stage T1N1M0 or T2–3N0–1M0 (SHAPIRO et al., 2015). Patients received neoadjuvant chemoradiotherapy based on carboplatin and paclitaxel followed by surgery or underwent surgery alone. Overall survival was 48.6 months in the neoadjuvant treated group and 24 months in the surgery group. Furthermore, 95% of the patients were able to complete the chemoradiotherapy regimen with low occurrence of adverse effects. Radical resection was achieved in 92% of the patients in the chemoradiotherapy group compared to 69% in the surgical group. Additionally, patients who underwent neoadjuvant chemoradiotherapy showed significantly less locoregional and distant progression. These results are in accordance with randomized clinical trials (RCTs), which reported increased rates of R0 resections, beneficial survival, and reduced incidence of local recurrence in patients treated with neoadjuvant chemoradiotherapy followed by surgery (CAO et al., 2009; TEPPER et al., 2008; VAN HAGEN et al., 2012).

2.6 Open Esophagectomy

Open esophagectomy (OE) with radical lymphadenectomy can be conducted transhiatal or transthoracic. In transhiatal esophagectomy, esophagus is mobilized and divided through the esophageal hiatus without thoracotomy. Then, after resection of the proximal stomach and lower/middle thoracic esophagus, the gastric conduit is pulled up through the posterior mediastinum until it reaches esophagus at the cervical level, where the cervical anastomosis is performed. On the other hand, transthoracic esophagectomy is conducted with two different surgical procedures. Ivor Lewis esophagectomy is performed through laparotomy and right thoracotomy, whereas McKeown esophagectomy is conducted through laparotomy, right thoracotomy, and cervical incision.

According to the German S3 guidelines, Ivor Lewis procedure consists the recommended approach for tumors in the middle and lower thoracic esophagus as well as in GEJ tumors type I (Siewert's classification). Ivor Lewis is not indicating in patients with esophageal tumors above the level of carina, since adequate resection margins cannot be achieved. On the other hand, McKeown esophagectomy is indicated in tumors of upper, middle, and lower thoracic esophagus.

Transhiatal esophagectomy is recommended for tumors located in GEJ type II and III (Siewert's classification). Specifically, in type II tumors, RCTs showed no survival benefits in patients treated with Ivor Lewis compared to transhiatal esophagectomy. Five-year and 10-year survival rates were 51% and 37% in the transhiatal group and 37% and 24% in the Ivor Lewis group, respectively (KUROKAWA et al., 2015). Consequently, for type II and III tumors, extended gastrectomy with transhiatal resection of distal esophagus is indicated.

2.7 Comparison Between Different Surgical Procedures

In western countries, a shift from the 3-stage operation (McKeown) in favor of the Ivor Lewis procedure has been documented (LUKETICH et al., 2012; MARKAR et al., 2015; MESSAGER et al., 2015). In a nationwide study in France with a total of 3,009 patients, Ivor Lewis procedure was conducted in 84% of the patients. McKeown and transhiatal esophagectomy were conducted in 9.7% and 6.3% of the patients, respectively (MESSAGER et al., 2015). The raise in Ivor Lewis operations has been attributed to the increased incidence of AC in the GEJ and lower esophagus as well as to an effort to reduce recurrent nerve injuries associated with the 3-stage approach (LUKETICH et al., 2012; VAN WORKUM et al., 2017). Since the majority of tumors are located in distal esophagus or in GEJ, R0 resection is oncologically feasible with Ivor Lewis surgery.

Compared to intrathoracic anastomosis, cervical anastomosis is technically less challenging. Furthermore, more proximal resection margin is achieved providing radical oncological resection. Anastomotic leak in cervical anastomosis can be managed easier than intrathoracic leak, which causes mediastinitis (VAN WORKUM et al., 2017). However, intrathoracic anastomosis is associated with lower incidence of anastomotic leakage, better functional results, and decreased tension at the level of anastomosis (LUKETICH et al., 2012). Decreased blood loss and shorter length of hospital stay have been reported in patients treated with Ivor Lewis compared to McKeown approach (VAN WORKUM et al., 2017). Incidence of pulmonary complications, benign strictures, and postoperative mortality are comparable between the two procedures. Oncological outcomes, including positive resection margins, tumour recurrence, disease-free and overall survival, are equivalent (BIERE et al., 2011; KASSIS et al., 2013).

The implementation of transhiatal esophagectomy has been decreased and replaced by transthoracic esophagectomy. In transhiatal esophagectomy, visualization higher up in mediastinum is reduced, and the mediastinal lymph node dissection is limited. On the contrary, transthoracic esophagectomy provides advanced oncological outcomes with enhanced lymphadenectomy in patients with adenocarcinoma of distal esophagus (OMLOO et al., 2007).

Taking all these points into consideration, Ivor Lewis approach is considered the preferred technique for middle and lower esophageal cancer, and GEJ tumors type I.

2.8 Complications of Open Esophagectomy

OE is associated with increased rate of postoperative complications, making it one of the procedures with the highest impact on patients' quality of life. The incidence of postoperative morbidity is estimated at 39-60% (MAMIDANNA et al., 2012; SIHAG et al., 2016). The majority of complications are related to the respiratory system with an incidence around 27–50%, followed by wound infection (15.5%), cardiovascular complications (11.2%), and anastomotic leak (2.5-10.2%) (MAMIDANNA et al., 2012; MARKAR et al., 2015). In-hospital and 30-day mortality is estimated at 3-7.3% (MAMIDANNA et al., 2012; MARKAR et al., 2015; MESSAGER et al., 2015; RAYMOND et al., 2016). Postoperative complications have been linked to increased mortality, longer hospital stay, increased readmission rate, decreased quality of life, and decreased survival.

Many factors are associated with the complicated postoperative course. OE is a demanding and technically challenging procedure. The extended surgical trauma with laparotomy and thoracotomy affects the postoperative course, causing increased acute-phase inflammatory and stress responses. Intraoperatively, single lung ventilation deteriorates the pulmonary function. Furthermore, history of smoking, preexisting lung diseases, and advanced age have been implicated to the increased rate of cardiopulmonary complications. The majority of patients are malnourished at the time of diagnosis, which is considered as an additional aggravating factor. Malnutrition weakens the immune response, impedes wound healing, and promotes muscle wasting (MARIETTE et al., 2012). Simultaneously, the altered anatomy following esophagectomy, including the resection of the lower esophageal sphincter, the partial resection of the stomach, and the vagotomy, constitutes an additional causing factor of postoperative malnutrition. Furthermore, several long-term functional disorders, such as delayed gastric emptying (DGE), gastroesophageal reflux, aspiration, dumping syndrome, diarrhea, loss of appetite, eating difficulties, and odynophagia, can deteriorate the postoperative course (HAVERKORT et al., 2010).

Taking into account the increased rate of complications, minimally invasive esophagectomy (MIE) has been developed with the aim to reduce the postoperative morbidity without compromising on the oncological outcomes. It is assumed that less surgical trauma could lead to better preserved acute-phase inflammatory and stress responses. The less invasive nature of the procedure may cause a lower incidence of postoperative complications.

2.9 Minimally Invasive Esophagectomy

Minimally invasive surgery emerged in the 1980s as a safe and effective technique. Since then, the use of minimally invasive procedures has been expanded widely in many surgical specialities, including colon, stomach, lung, liver, and esophageal surgery. Studies have reported that minimally invasive surgeries are associated with less blood loss, controlled pain, reduced stay in intensive care unit (ICU), decreased pulmonary complications, shorter length of hospital stay, and better quality of life compared to open procedures (BUIA et al., 2015; LI et al., 2016).

MIE was introduced in the 90s' with the aim to reduce postoperative morbidity without compromising on oncological safety (CUSCHIERI et al., 1992). Initially, MIE was indicated in the treatment of localized (classified as T1 or T2) and not neoadjuvant treated tumors (AKAISHI et al., 1996; GOSSOT et al., 1993). However, in the last few years, MIE has been developed rapidly, constituting a treatment approach for neoadjuvant treated and advanced tumors (MAMIDANNA et al., 2012; MESSAGER et al., 2015).

Ivor Lewis procedure can be conducted as hybrid (HMIE) or as total minimally invasive esophagectomy (TMIE). In hybrid Ivor Lewis approach, gastric mobilization and abdominal lymphadenectomy are performed laparoscopically, whereas tumor resection and anastomosis are conducted through right thoracotomy. TMIE is conducted laparoscopically and thoracoscopically. McKeown operation can be conducted as hybrid technique with laparoscopy, thoracotomy, and cervical incision. Total minimally invasive McKeown operation includes laparoscopy, thoracoscopy, and cervical anastomosis. Minimally invasive transhiatal esophagectomy has been described, where laparotomy is replaced by laparoscopy (Figure 3).

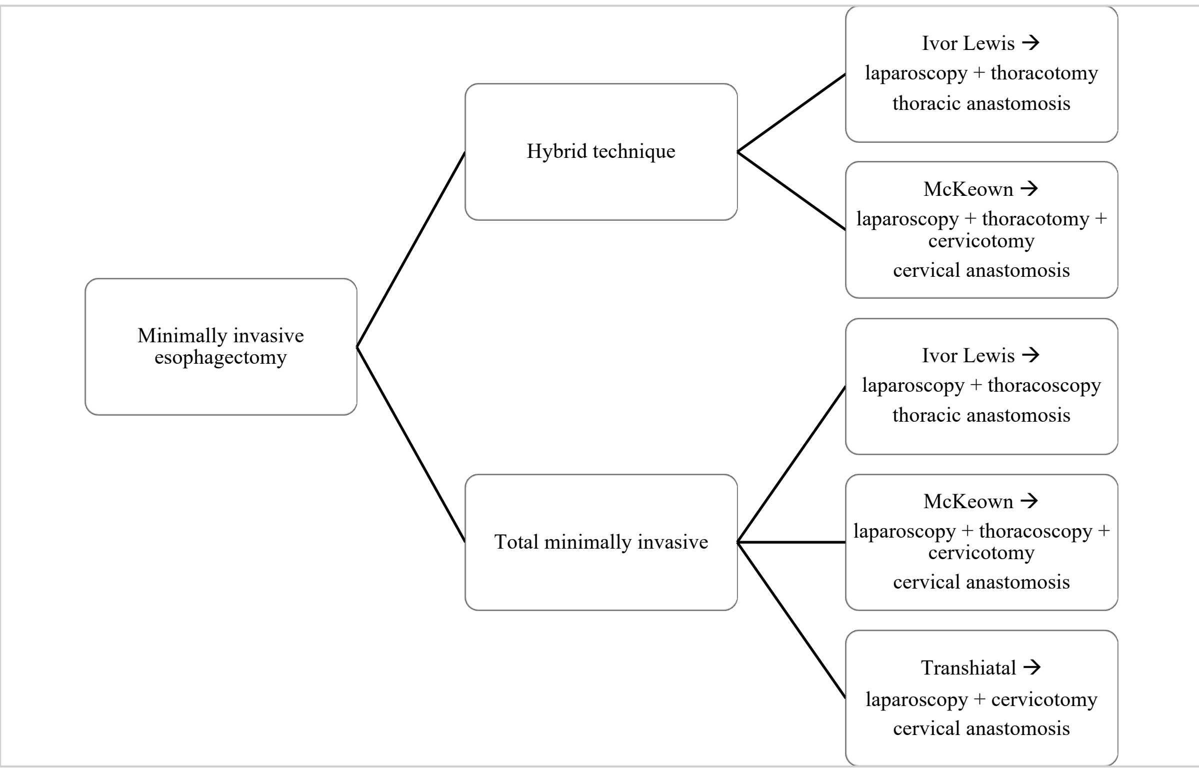

Figure 3: Different types of minimally invasive esophagectomy. Esophagectomy can be conducted as hybrid or as total minimally invasive procedure.

2.10 Ivor Lewis Esophagectomy: HMIE vs. TMIE

Apply of total minimally invasive Ivor Lewis approach is not widespread due to difficulties in performing the thoracoscopic anastomosis. In a RCT, 44% of the patients in the TMIE group required endoscopic treatment for symptomatic stenosis of the anastomosis (STRAATMAN et al., 2017). In a population based national study, TMIE was associated with increased rates of postoperative reinterventions, including endoscopic, radiologic, and surgical procedures, compared to HMIE (MAMIDANNA et al., 2012). Other reported advantages of HMIE over TMIE are the reasonable learning curve, the reproducibility, the absence of laparoscopic or thoracoscopic tumor resection, and the avoidance of tumoral dissemination.

Moreover, HMIE includes the advantages of laparoscopy, such as decreased inflammatory response to surgical trauma, reduced muscular stress, and lower albumin and fluids loss. Reduction of inflammatory factors such as interleukin, procalcitonin, liver enzyme, and lactate levels could be associated with decrease in postoperative complications, such as pneumonia, sepsis, and wound infection.

Hybrid technique was introduced in 2016 as a surgical approach for EC in the Clinic of General, Visceral, Vascular, and Pediatric Surgery in Homburg/Saar, in Germany.

2.11 Aim of the Study

Retrospective studies have been conducted to evaluate the role of HMIE in the treatment of EC. The majority of these studies have limitations, such as noncomparable groups and selection bias. Many studies have not utilized wide accepted definitions for complications making difficult a systematic comparison between different studies. Additionally, the influence of learning curve on the perioperative outcomes has been poorly evaluated.

HMIE is considered a complex surgery and superiority over OE is controversial. Although some studies have documented reduced incidence of postoperative morbidity in favor of HMIE (BJELOVIC et al., 2016; BRIEZ et al., 2012) , other surveys failed to detect superiority of HMIE over OE, revealing comparable or worse outcomes (MAMIDANNA et al., 2012; SGOURAKIS et al., 2010). At the same time, the number of RCTs is limited. The MIRO-trial demonstrated beneficial short-term outcomes following HMIE (MARIETTE et al., 2019), whereas increased rates of anastomotic stenosis requiring intervention were reported in the TIME-trial (STRAATMAN et al., 2017). Consequently, although prospective and retrospective studies have been conducted, the safety and efficacy of HMIE are not well documented. For that reason, the german S3 guidelines do not recommend hybrid or total minimally invasive esophagectomies as standard procedures in the treatment of EC.

We conducted this survey under the hypothesis that the hybrid approach through laparoscopy and thoracotomy results in reduced postoperative complications with equivalent oncological outcomes in two similarly matched groups of patients. The first 17 hybrid esophagectomies, which were conducted in our institution, were included in the analysis in order to show that the new approach is not associated with increased learn-curve morbidity and mortality.

3 Materials and Methods

3.1 Study Design and Data Collection

HMIE was introduced in the University Hospital of Saarland in August 2016. Prior to this point, patients were operated with OE, which was conducted as Ivor Lewis, McKeown, or transhiatal. We conducted a retrospective cohort study to compare HMIE with OE as Ivor Lewis for patients with EC.

This study included the first 17 patients who underwent laparoscopic esophagectomy with open intrathoracic end-to-side anastomosis at a high-volume tertiary center between August 2016 and December 2019. All operations were conducted by two surgeons. Surgeries were conducted by physicians experienced in OE preventing a surgeon bias. Our hospital is thought a high-volume center with more than 20 esophagectomies per year, preventing an institution bias.

This group of patients was compared with patients who underwent traditional open thoraco-abdominal esophagectomy as Ivor Lewis in our clinic. OEs conducted by the two surgeons between 2015 and 2019 were retrieved. Exclusion criteria were:

- esophagectomy with colonic interposition,
- transhiatal esophagectomy,
- McKeown esophagectomy,
- esophagectomy for benign disease,
- emergeny esophagectomy for complicated EC,
- pediatric patients,
- surgical procedure conducted by other surgeons in our department,
- esophagectomies conducted before 2015,
- and discharge against medical advice.

Propensity score matching method was utilized to reduce selection bias by creating two groups with similar preoperative characteristics. Propensity scores were generated using the covariates of age, BMI, pulmonary comorbidity, cardiac comorbidity, histologic tumor type, and neoadjuvant treatment. Patients in the HMIE group were matched with 17 patients in the OE group using a 1:1 ratio and the nearest-neighbour score matching.

The study was approved by the Medical Ethics Committee of the Medical Association of Saarland (file number: 259/19).

3.2 Staging and Preoperative Work-up

Patients were considered to be operable after a complete pretherapeutic work-up, which includes esophagogastroduodenoscopy (EGD) with biopsies, contrast-enhanced computed tomography (CT) scan of thorax and abdomen, and endoscopic ultrasound (EU). If indicated, positron emission tomography (PET) or positron emission tomography-computed tomography (PET-CT) were performed.

Clinical staging (cTNM) was based on the data obtained from the EGD, CT scan, EU, and in some cases from PET. Computed tomographic scans were performed in all cases to rule out metastatic or local disease that is not resectable.

All cases were discussed in the interdisciplinary cancer conference. Neoadjuvant chemoradiotherapy was recommended for T2-4 tumors and in cases of suspected nodal disease. Neoadjuvant chemoradiotherapy was performed according to the CROSS or FLOT protocol. After neoadjuvant treatment, patients were restaged by contrast-enhanced CT scan of thorax and abdomen. OE and HMIE were performed four to six weeks after completion of chemoradiotherapy. In selected cases, ventricular function was estimated with echocardiography or dynamic test. Pulmonary function test was conducted in patients with preexisting pulmonary disease.

Patients received perioperatively epidural catheter, central venous catheter, and arterial line. Antibiotics (third-generation cephalosporin and metronidazole) were administrated intraoperatively. A nasogastric tube was placed for the decompression of stomach.

3.3 Description of the Procedure

3.3.1 HMIE

All patients underwent Ivor-Lewis procedure. Surgical technique has been standardized. Patients underwent transthoracic en bloc esophagectomy with intrathoracic termino-lateral anastomosis. Extended two field lymphadenectomy was performed according to the lymph node map of the Japanese Society for Esophageal Diseases. The abdominal approach differs between the two groups. In the HMIE group, gastric mobilization and lymphadenectomy are performed laparoscopically, whereas gastric mobilization and construction of the gastric conduit are conducted during laparotomy in the OE group. The technical steps of transthoracic hybrid esophagectomy are described below.

Patient positioning and trocar placement

In the HMIE group, patient is placed in a supine position, in a 20- to 30-degree reverse Trendelenburg lithotomy position (Figure 4). The operating surgeon stands between the patient's legs. The first and the second assistant stand on the left and right side of the patient, respectively. A pneumoperitoneum (13-15mmHg) is established. Five ports are inserted (12mm optic port at the umbilicus, 12mm port for stapling, clipping, or dissection, 5mm port for the retractor of left liver lobe, and two 5mm ports for traction and grasping) as shown in Figure 5.

Figure 4: Patient is placed in a 20- to 30-degree reverse Trendelenburg lithotomy position.

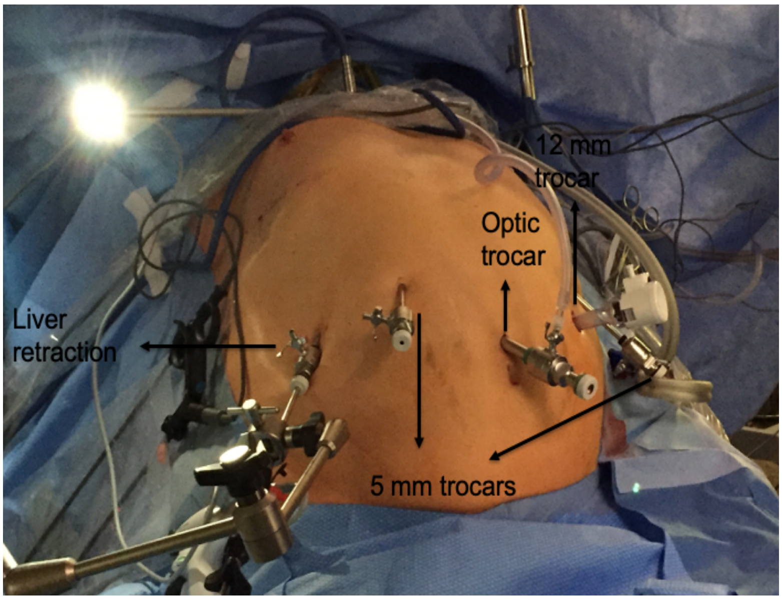

Figure 5: Trocar placement.

Crural visualization and mobilization of distal esophagus

Abdomen is explored to exclude advanced metastatic disease. The gastrohepatic ligament is dissected and the right crus is visualized. Then, the left crura of the diaphragm is visualized.

The right crura is not usually dissected or is minimally dissected in order to decrease the risk of postoperative hiatal hernia. The distal esophagus is divided en bloc with the LN as far as possible towards mediastinum.

Mobilization of stomach

The greater curvature of the stomach is mobilized by dissecting the gastrocolic ligament with harmonic scalpel. The left and right gastro-epiploic arcade are preserved (Figure 6). Dissection is performed parallel to the gastro-epiploic arcade until the short gastric vessels are identified. The short gastric vessels are transected, and the stomach is mobilized from the spleen and left crura.

LN at the left gastric artery origin are dissected en bloc with the stomach. The left gastric vessels (left gastric artery, vena coronary ventriculi) are dissected close to celiac trunk and deposited with clips. Lymphadenectomy is performed along the common hepatic artery, at celiac truck, and at proximal splenic artery. LN in left and right paracardial region are divided en bloc with esophagus. Pyloromyotomy or pyloroplasty are not performed. Port incisions are closed after removing the trocars under direct vision. The fascia of the 12mm ports is closed with 0-vicryl suture.

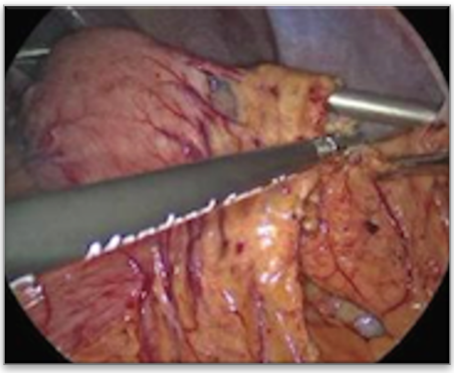

Figure 6: The greater curvature of the stomach is mobilized by dividing the gastrocolic omentum with harmonic scalpel and by preserving the link and right gastro-epiploic arcade.

Thoracotomy and resection of esophagus

In HMIE, the thoracic approach includes the construction of the gastric conduit. The right lung is excluded with selective intubation. The patient is turned to the left lateral position. A 10-12 cm postero-lateral thoracotomy is performed in the 4th intercostal space. The inferior pulmonary ligament is divided. Incision of mediastinal pleura is performed on both sides of esophagus up to the level of the arch of azygos vein. The arch of azygos vein is then dissected at its junction with the superior vena cava.

Esophagus is mobilized up to the level of diaphragm along with the periesophageal tissue and LN. Then, esophagus is resected en bloc with the surrounding tissues and nodes. The division of esophagus is performed high above the azygos vein with a safety margin of at least 2 cm. Mediastinal lymphadenectomy includes the region of thoracic paratracheal, subcarinal, left and right bronchial, lower posterior mediastinal, and para-esophageal LN.

The previously mobilized stomach is retrieved through hiatus in the chest. A gastric conduit with 4 to 5 cm wide is constructed with serial firings of 40-50 mm Endo-GIA® cartridges on the distal lesser curvature of the stomach proximally to the mid-portion of the gastric fundus. Specifically, across the lesser curvature and cranial to the third branch of the right gastric artery is applied the first cartridge. Division is directed towards the greater curve. Consistent width of the stomach is required, whereas spiralization of the gastric tube during application of cartridges is avoided. Furthermore, interrupted 4-0 PDS stitches are applied at the intersection of the staple lines. Pyloric dilation is carried out manually with a large clamp intraluminally. The end-to-side esophagogastric anastomosis is performed at the apex of the right chest using 29 mm EEA® circular stapler (Figure 7). Interrupted 3-0 PDS sutures are applied at the anastomosis. The thoracic duct is not ligated routinely. A nasogastric tube is placed in the gastroplasty. The chest is closed after placement of one or two right-sided chest drains. A left-sided chest drain is not placed routinely. Jejunostomy catheter is not placed routinely for postoperative feeding and is restricted for cachectic patients who might benefit from additional nutrition support.

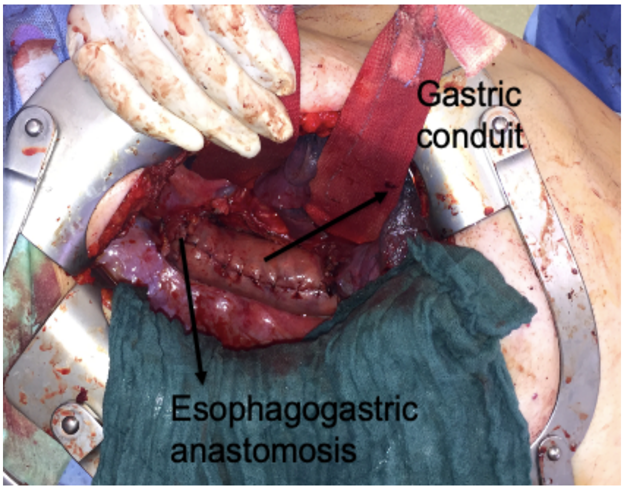

Figure 7: The end-to-side esophagogastric anastomosis is performed at the apex of the right chest using 29 mm EEA® circular stapler. Interrupted 3-0 PDS sutures are applied at the anastomosis. Interrupted 4-0 PDS stitches are applied at the intersection of the staple lines.

Lymphadenectomy in HMIE

In our series, two-field lymphadenectomy was conducted in the HMIE and OE group, according to the Japanese Classification of Esophageal Cancer (Figure 8). Two-field lymphadenectomy is recommended as the standard approach in the German S3 guidelines.

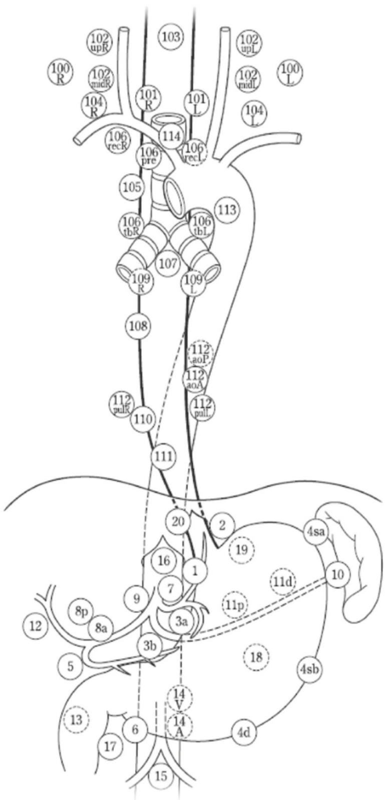

Figure 8: Lymphadenectomy is conducted according to the Japanese guidelines (Source: Japanese Classification of Esophageal Cancer, 11th Edition, part I). The following LN are divided in Ivor Lewis procedure for EC located in lower esophagus or GEJ:

Intraabdominal LN:

20: LN in the esophageal hiatus of the diaphragm

1: Right paracardial LN

2: Left paracardial LN

7: LN along the left gastric artery

3a: Lesser curvature LN along the branches of the left gastric artery

9: LN along the celiac artery

19: Infradiaphragmatic LN

11p: LN along the proximal splenic artery

8a: LN along the common hepatic artery

Intrathoracic LN:

110: Lower thoracic paraesophageal LN

111: Supradiaphragmatic LN

112: Posterior mediastinal LN

108: Middle thoracic paraesophageal LN

109: Main bronchus LN left and right

3.3.2 OE

In OE, midline supraumbilical laparotomy is performed. The mobilization of the stomach is achieved in the same way as in the laparoscopic procedure. The gastrohepatic ligament is divided, the phreno-esophageal ligament is incised, and esophagus is circumferentially dissected. Although incision of the crura is usually avoided, in case of insufficient mobilization of esophagus, hiatus is widened by incising the right crura. The greater curvature is mobilized as in the laparoscopic procedure. However, in OE, the gastric conduit is constructed during laparotomy. Then, the gastric conduit is sewn back to the distal esophagus with a single suture to facilitate retrieval within the chest.

The thoracic approach includes the construction of the anastomosis. Esophagus is mobilized up to the level of diaphragm along with the periesophageal tissue and LN. Then, esophagus is resected en bloc with the surrounding tissues and nodes. The division of esophagus is performed high above the azygos vein with a safety margin of at least 2 cm. The gastric conduit is retrieved through the hiatus in the chest. The end-to-side esophagogastric anastomosis is performed at the apex of the right chest using 29 mm EEA® circular stapler. Interrupted 3-0 PDS sutures are applied at the anastomosis.

3.4 Postoperative Care

Extubation usually occurs in the operating room, and patients are transferred to the ICU. Patients receive epidural analgesia during the first four to five postoperative days. If epidural analgesia is unsuccessful, patient-controlled analgesia with intravenous opioids is administrated. Six hours after the end of the procedure, thromboprophylaxis with unfractionated heparin can be commenced. Pulmonary physiotherapy and parenteral nutrition comprise the first postoperative measures. Parenteral nutrition is administrated until patients are able to consume an oral diet that covers at least 60% of their daily needed caloric intake (25-30 kcal/kg/day). Antibiotic prophylaxis is not administrated postoperatively.

Patients are maintained nil per os until the fifth postoperative day. On the fifth day, gastrografin swallow examination is performed. If anastomotic leakage and motility disorder are not demonstrated, the nasogastric tube is removed, and oral intake is progressively introduced.

Patients are discharged from the hospital when laboratory and clinical evidence of infection is absent, patients are able to ambulate without assistance, no major analgesics are required, and oral diet is well tolerated without gastrointestinal symptoms.

3.5 Histological Analysis

Histological analysis includes tumor histological type, TNM classification, radicality of resection (R0, R1, or R2), vertical and lateral margins, tumoral differentiation, and tumor regression grade if neoadjuvant treatment was performed. The 8th edition of AJCC guidelines was utilized for the pTNM classification. As pathologic complete response is defined the absence of residual tumor cells and positive LN in the resected specimen.

In the 8th edition of AJCC guidelines, a new classification was introduced for patients who had undergone neoadjuvant treatment and surgical resection. Postneoadjuvant staging (ypTNM) includes histopathological categories which were not described in the pTNM staging, such as T0N0-3M0.

Since no all patients had undergone neoadjuvant treatment, histologic classification was conducted according to the pTNM staging. Pathologic specimens with no residual tumor were classified as ypTNM stage I, since pTNM staging does not include tumors with complete histological response (T0, N0, M0) following neoadjuvant treatment.

3.6 Definition of Outcomes

3.6.1 Primary Outcomes

Surgical and oncological results were included in the primary outcomes of our analysis. Intraoperative data, such as operative time, blood transfusion, and conversion rate to open procedure, were evaluated. Stay in ICU and length of hospital stay were compared between the two groups. Readmission rate in our department as well as in the ICU were recorded. Reoperations and reinterventions were compared between the two groups.

In-hospital and 30-day mortality were reported in the study. Thirty-day mortality included patients who died in hospital, at home after discharge, those transferred to other care facilities, or in a convalescent environment. Number of retrieved LN and resection status were included in the oncological outcomes.

Postoperative complications were defined and recorded according to the guidelines of the Esophageal Complications Consensus Group (ECCG) (LOW et al., 2015). The ECCG has developed a standardized list for recording perioperative complications associated with esophagectomies (Table 4). Furthermore, complications were categorized according to the Clavien-Dindo classification (Table 5). This classification defines the postoperative complications depending on severity as grade II (pharmacological treatment, blood transfusion, or parenteral nutrition is required), grade III (surgical, endoscopic, or radiological intervention is required), grade IV (life-threatening complication with single organ or multiorgan dysfunction), and grade V (death) (DINDO et al., 2004). All complications occurring within 30 days of surgery or during the hospital stay were included in our analysis.

According to the Clavien-Dindo classification, as grade I complication is defined any deviation from the normal postoperative course without need for pharmacological treatment or surgical, endoscopic, and radiological intervention. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. Wound infections opened at the bedside are defined as grade I complications. The retrospective design of our study does not allow the recording of drug administration, such as antipyretics or analgetics, which do not influence the postoperative course. Consequently, patients who had not undergone a prolonged pharmacological treatment or an intervention were assessed as patients with uncomplicated postoperative course.

Surgical and gastroenterological complications, which were included in our study according to the ECCG guidelines, are demonstrated in Table 4. Esophageal leak, conduit necrosis, chyle leak, and recurrent nerve palsy were defined according to the ECCG guidelines. Each of these complications is stratified in three types based on the treatment.

Anastomotic leak is defined as a defect in anastomosis or staple line. Type I leak requires no intervention and is treated conservatively with medications or dietary modification. Localized defect requiring intervention, such as stent, Vacuum Assisted Closure therapy (VAC), or image-guided percutaneous drainage, is defined as Type II. Finally, as Type III anastomotic leak is defined any defect that is treated surgically.

Focal conduit necrosis that is diagnosed endoscopically without indication for surgical therapy is defined as Type I. Focal conduit necrosis without leakage that is treated surgically without esophageal diversion is recorded as Type II. This complication is defined as Type III when gastric conduit resection and esophageal diversion are required.

Chyle leak is categorized according to output and treatment method. Chyle leak is defined as level A when the output is less than 1 litre per day and B when it is more than 1 litre. According to the treatment approach, chyle leak is defined as Type I when conservative therapy with dietary modifications is required. Type II and III chyle leak are treated with parenteral nutrition and surgical procedure, respectively.

Transient vocal cord injury requiring no therapy is defined as Type I. Injury that requires elective surgical treatment is defined as Type II, whereas in Type III injury, acute surgical intervention is indicated. The severity level is A for unilateral injury and B for bilateral.

As gastric conduit retention or DGE is defined a motility disorder of the stomach, which requires pharmacological treatment or intervention, such as EGD with pyloric balloon dilation, intramuscular quadrant injection of Botulinum toxin, or pyloric stent. The diagnosis of DGE is based on clinical symptoms and radiologic or endoscopic findings. Patients with clinically suspected symptoms of DGE, such as dysphagia, regurgitation, and rapid satiety, undergo radiography (CT or contrast enema X-ray) to establish the diagnosis. In our series, postoperative DGE was included in complications when it was associated with prolonged hospital stay or was treated with oral or intravenous prokinetic agents.

As postoperative pulmonary complications were included pneumonia, pleural effusion, pleural empyema, pneumothorax, pulmonary edema, atelectasis, acute respiratory distress syndrome (ARDS), respiratory insufficiency, and tracheobronchial injury (Table 4).

Pneumonia was defined using existing internationally accepted criteria by the Infectious Diseases Society of America (KALIL et al., 2016). According to this definition, pneumonia is defined as a new pulmonary opacity or lobar consolidation with air bronchograms on chest radiography with the presence of at least two of the following laboratory and clinical findings: leukocyte count greater than 10.000/mm^3 or fewer than 1.500/mm^3, fever or temperature less than 35°C, arterial oxygen desaturation, and positive respiratory samples.

Pleural effusion and pneumothorax were considered as complications when chest drainage was required. Atelectasis leading to bronchoscopy and respiratory insufficiency leading to reintubation were included in complications. ARDS was defined according to the Berlin definition (FORCE et al., 2012). ARDS is characterized by timing of onset, radiographic features, and origin of edema. Severity level is based on the PaO_2/FiO_2 ratio on 5cm of continuous positive airway pressure. ARDS is categorized as mild (PaO_2/FiO_2 = 200-300), moderate (PaO_2/FiO_2 = 100-200), and severe ($PaO_2/FiO_2 \leq 100$).

3.6.2 Secondary Outcomes

Cardiac, urologic, thromboembolic, neurologic complications, and infections are included in the secondary outcomes (Table 4). Myocardial infarction is defined according to the World Health Organization criteria (MENDIS et al., 2011). Delirium is defined according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) classification. Sepsis or a new-onset organ failure are defined according to the Sepsis-related Organ Failure Assessment (SOFA) score (VINCENT et al., 1996).

Table 4: Postoperative complications according to the standardized list for recording complications associated with esophagectomies developed by the ECCG.

Postoperative complications
Surgical and gastrointestinal complications
1. Esophagogastric leak at anastomosis or staple line
2. Anastomotic stricture
3. Conduit necrosis
4. Gastric conduit retention or delayed gastric emptying
5. Wound infection requiring surgical intervention
6. Intrathoracic/intraabdominal/mediastinal abscess
7. Thoracic wound dehiscence
8. Abdominal wall dehiscence
9. Diaphragmatic hernia
10. Chyle leak

11. Mediastinitis
12. Gastrointestinal bleeding requiring intervention or transfusion
13. Recurrent nerve injury
14. Paralytic or mechanical ileus
15. Clostridium difficile infection
16. Pancreatitis
17. Liver dysfunction
Pulmonary complications
1. Pneumonia
2. Pleural effusion requiring drainage
3. Pneumothorax requiring chest drainage
4. Pleural empyema
5. Pulmonary edema
6. Atelectasis requiring bronchoscopy
7. Respiratory failure requiring reintubation
8. Acute respiratory distress syndrome (Berlin Definition)
9. Tracheobronchial injury
Cardiac complications
1. Cardiac arrest requiring CPR
2. Myocardial infarction (Definition: World Health Organization)
3. Dysrhythmia atrial requiring treatment
4. Dysrhythmia ventricular requiring treatment
5. Congestive heart failure requiring treatment
6. Pericarditis requiring treatment
Urologic complications
1. Acute renal insufficiency
2. Urinary tract infection
3. Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter
Thromboembolic complications
1. Deep venous thrombosis
2. Pulmonary embolism
3. Stroke
4. Peripheral thrombophlebitis
Neurologic complications
1. Acute delirium (Definition: Diagnostic and Statistical Manual of Mental Disorders)
Infection
1. Generalized sepsis
2. Other infections requiring antibiotics

3. Multiple organ dysfunction syndrome (MODS)

Table 5: The Clavien-Dindo Classification for surgical complications.

Clavien-Dindo Classification	
Grade	**Definition**
I	Any deviation from the normal postoperative course without the need for surgical, endoscopic, or radiological procedure. Acceptable therapeutic regimens are medications such as antiemetics, antipyretics, analgesics, diuretics, and electrolytes. Wound infections opened at the bedside are included.
II	Complications requiring pharmacological treatment with medications other than such allowed for grade I complications. Blood transfusions and parenteral nutrition are included.
III	Complications requiring surgical, endoscopic, or radiological intervention.
III-A	No general anesthesia.
III-B	Interventions under general anesthesia.
IV	Life-threatening complications (including complications of the central nervous system) requiring intermediate care or ICU management.
IV-A	Single organ dysfunction.
IV-B	Multiple organ dysfunction.
V	Death of patient.
Suffix "D"	This suffix is added to indicate the need for follow-up to evaluate the complication after the discharge.

3.7 Propensity Score Matching Analysis

Propensity score matching analysis was used to remove bias attributed to observational studies. Propensity score is a statistical matching analysis that attempts to estimate the effect of a treatment by accounting for the covariates that predict receiving the treatment. Propensity score matching attempts to reduce the selection bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcomes among units that received the treatment versus those that did not.

The propensity score is designed to mimic some of the characteristics of randomized trials in the context of a retrospective study. To this end, a logistic regression model for binary response variables has been fitted with age, BMI, pulmonary comorbidities, cardiac comorbidities, histologic type, and neoadjuvant treatment as covariates. From this model, the conditional probability of assignment to the laparoscopic group was calculated and used as the propensity score. This score was then used to provide a 1:1 match in the two groups by using the nearest neighbour score matching without replacement.

Propensity score matching analysis was performed using the R language for statistical computing.

3.8 Statistical Analysis

Statistical analysis has been performed utilizing SPSS® version 20.0 software (IBM, Armonk, New York, USA). Quantitative variables are presented as median and interquartile ranges (IQR), and qualitative variables as percentages, absolute numbers, and ranges. The Fisher's exact test and the Pearson Chi-Square test have been utilized to identify statistically significant differences in categorical outcomes. For continuous variables, differences between the groups have been identified by the two-sample Wilcoxon rank-sum test.

Univariate analysis for the effects of selected predictive factors on pulmonary complications has been carried out by the Fisher's exact test. Multivariate analysis consists of a multiple logistic regression model. Results are presented as Odds Ratios (OR), 95% confidence intervals (CI), and p-values. All p-values are 2-sided. P-value equal or less than 0,05 is considered significant.

4 Results

4.1 Participants

This study included the first 17 patients who underwent laparoscopic esophagectomy with open intrathoracic end-to-side anastomosis at a high-volume tertiary center between August 2016 and December 2019. This group of patients was compared with patients who underwent traditional open thoraco-abdominal esophagectomy as Ivor Lewis in our clinic. The two surgeons conducted a total of 37 open esophagectomies between 2015 and 2019. Four patients underwent transhiatal esophagectomy and were excluded from our analysis. Furthermore, three patients underwent open Ivor Lewis esophagectomy for benign disease and were excluded. One patient was excluded, as he was discharged against medical advice (Figure 9, Appendices).

A total of 46 patients were included for analysis. Twenty-nine patients were treated with open procedure and 17 with hybrid esophagectomy. Propensity score matching method was utilized to reduce selection bias by creating two groups with similar preoperative characteristics. Propensity scores were generated using the covariates of age, BMI, pulmonary comorbidity, cardiac comorbidity, histologic tumor type, and neoadjuvant treatment. Patients in the OE group were matched with 17 patients in the HMIE group using a 1:1 ratio and the nearest-neighbour score matching.

By 1-to-1 propensity score matching, 17 pairs of patients in the OE and HMIE group were selected for inclusion. Figure 10 shows the distribution of propensity scores in the unmatched and matched groups.

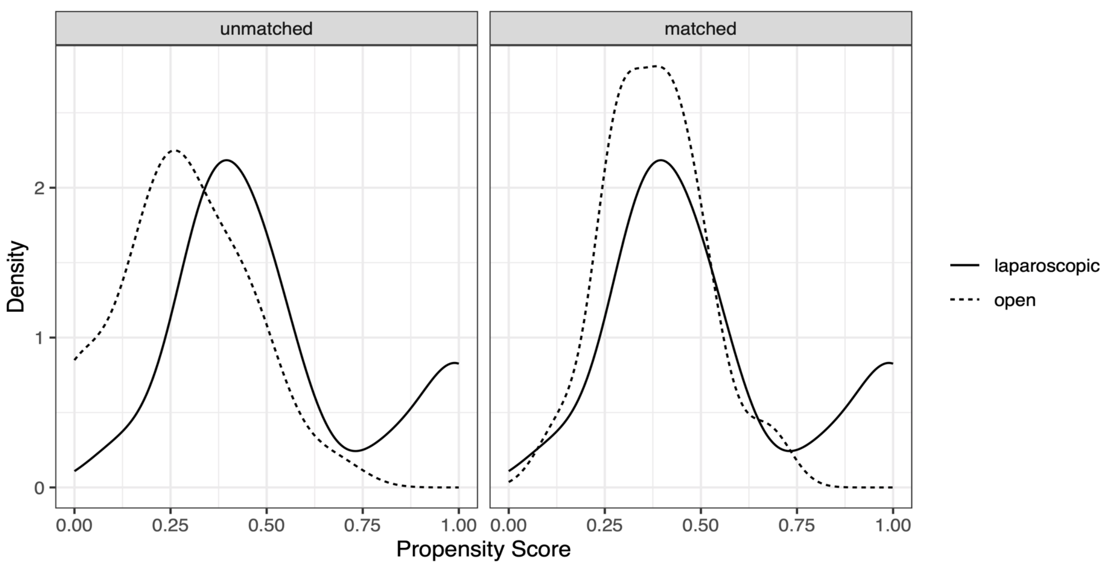

Figure 9: Distribution of propensity scores in the unmatched and matched patients.

4.2 Baseline Chracteristics

A total of 34 patients were included in the retrospective study. Seventeen patients were allocated in the HMIE and OE group, respectively. The preoperative baseline characteristics are displayed in Table 6. Both groups are well balanced for the variables age, BMI, pulmonary comorbidities, cardiac comorbidities, histologic type, (y)pTNM, and neoadjuvant treatment. The median age at the time of surgery was 63 years (IQR, 58-70 years). The median age was 64 and 60 years in the OE and HMIE group, respectively ($p = 0.26$). The majority of patients were males in both groups; however, in the OE group, males were statistically more than in the HMIE group (OE: n = 16 vs. HMIE: n = 11, $p = 0.034$). The median BMI was 26.3 kg/m^2 (IQR, 22.8-30.7 kg/m^2).

Statistically significant differences were not found in the baseline characteristics between the two groups. Tumor characteristics, such as tumor location, histological type, and pathologic stage, were similar. The majority of patients were diagnosed with tumors in the lower third of esophagus, including tumors of the GEJ. Six patients with tumors located in the middle thoracic esophagus were included in our survey (OE: n = 4 vs. HMIE: n = 2, $p = 0.368$). Pathological analysis revealed AC and SCC in 14 and three patients in both groups, respectively.

The majority of patients underwent neoadjuvant therapy, which was chemoradiation according to CROSS or FLOT protocol (OE: n = 13 vs. HMIE: n = 13, $p = 1.00$). All cases were discussed in the interdisciplinary cancer conference, and primary resection without neoadjuvant treatment was decided for seven patients. One patient was advised to receive neoadjuvant treatment but refused to follow the treatment. Histopathological analysis revealed stage I (pTNM) esophageal cancer in 41.2% of the patients, stage II in 11.8%, and stage III and IV in 14.7%, respectively. Complete pathological response to neoadjuvant treatment, which is defined as ypTNM stage I, was observed in six patients (17.6%).

Furthermore, differences in preexisting comorbidities were not found. Cardiovascular and pulmonary preexisting diseases were comparable between the two groups. Pulmonary and cardiac comorbidities were present in 20.6% and 23.5% of the patients, respectively. Specifically, 14.7% of the patients suffered from chronic obstructive pulmonary disease (COPD) and 5.9% from asthma. The OE and HMIE groups were homogeneous in terms of patient- and tumor-related data.

Table 6: Preoperative baseline characteristics. Comparison of demographic, clinical, and tumor characteristics. The OE and HMIE groups were homogeneous in terms of patient- and tumor-related data.

Baseline characteristics						
	Unmatched patients			Matched patients		
Characteristic	**OE (n = 29)**	**HMIE (n = 17)**	**p value**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**
Age (median [IQR], years)	66 (58–70)	60 (56–64)	0.15	64 (58–70)	60 (56–64)	0.26
BMI (median [IQR], kg/m^2)	25.7 (24.2–29.4)	25.6 (22.7–31.6)	0.71	27.1 (24.6–29.4)	25.6 (22.7–31.6)	0.52
Pulmonary comorbidity, n (%)			0.81			1.00
Asthma	2 (6.9%)	1 (5.9%)	1.00	1 (5.9%)	1 (5.9%)	1.00
COPD	5 (17.2%)	2 (11.8%)	0.45	3 (17.6%)	2 (11.8%)	1.00
OSAS	2 (6.9%)	0	0.50	0	0	1.00
Cardiac comorbidity, n (%)			0.11			0.26
Arrhythmia	0	3 (17.6%)	0.25	0	3 (17.6%)	0.25
Coronary artery disease	3 (10.3%)	2 (11.8%)	1.00	3 (17.6%)	2 (11.8%)	1.00
Heart failure	2 (6.9%)	0	0.50	0	0	1.00
(y)pTNM-Classification, n (%)			0.25			0.48
ypTNM Stage I (T0, N0)	3 (10.3%)	4 (23.5%)	1.00	2 (11.8%)	4 (23.5%)	0.69
pTNM Stage I	9 (31%)	8 (47.1%)	1.00	6 (35.3%)	8 (47.1%)	0.79
pTNM Stage II	6 (20.7%)	1 (5.9%)	0.13	3 (17.6%)	1 (5.9%)	0.63
pTNM Stage III	7 (24.1%)	1 (5.9%)	0.07	4 (23.5%)	1 (5.9%)	0.37
pTNM Stage IV	4 (13.8%)	3 (17.6%)	1.00	2 (11.8%)	3 (17.6%)	1.00
Histologic Type, n (%)			0.723			1.00
AC	22 (75.9%)	14 (82.4%)	0.606	14 (82.4%)	14 (82.4%)	1.00
SCC	7 (24.1%)	3 (17.6%)	0.606	3 (17.6%)	3 (17.6%)	1.00
Neoadjuvant treatment, n (%)	24 (82.8%)	13 (76.5%)	0.71	13 (76.5%)	13 (76.5%)	1.00

Continuous data are summarized by medians and IQR. For categorical variables, absolute numbers and percentages are computed. Differences between the open and laparoscopic group were investigated by Fisher's exact test (for categorical variables) and two-sample Wilcoxon rank-sum test (for continuous variables). All p-values are 2-sided.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; IQR, interquartile ranges; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome AC, adenocarcinoma; SCC, squamous cell carcinoma)

4.3 Operative and Postoperative Outcomes

The median operative time was 296 minutes (IQR, 275-330 min.). Statistically significant differences in the median operative time between the open and hybrid approach were not found (OE: 295 min. vs. HMIE: 297 min., $p = 0.418$). Length of stay in the ICU was statistically longer in the HMIE group (OE: 3 days vs. HMIE: 5 days, $p = 0.028$). However, although the HMIE group spent more time in the ICU, the length of hospital stay was comparable between the groups. Statistical analysis revealed no significant differences (OE: 15 days vs. HMIE: 16 days, $p = 0.425$). We should mention that ICU stay includes the stay in our intermediate care unit (IMCU), where patients undergo intensive physiotherapy and early mobilization.The in-hospital and 30-day mortality rate was zero in our survey. The rate of intra- and postoperative blood transfusions was similar in both procedures.

Two patients in the HMIE group were readmitted in the ICU during hospital stay (OE: n = 0 vs. HMIE: n = 2, $p = 0.485$). Furthermore, we investigated the readmission rate in our clinic for the included patients until the end of the study in December 2019. Patients who readmitted for reasons associated with the surgical procedure were included in this analysis. Three patients were readmitted in our clinic during this time period. Two patients were presented with increasing symptoms of dysphagia and reflux. Esophagogram demonstrated an intact anastomosis without stenosis, efficient emptying of contrast into duodenum, and slight degree retention in the gastric conduit attributed to vagal denervation. EGD was performed revealing reflux esophagitis. Thus, anti-reflux treatment was initiated, and patients were discharged with relief of symptomatic. The third patient readmitted because of hemorrhagic shock and hematemesis. Acute bleeding in the area of anastomosis was managed with endoscopic application of hemostatic powders and clips. Furthermore, pleural empyema was demonstrated in the contrast-enhanced CT, which was managed with thoracotomy and placement of two chest drains. Although all patients who readmitted in our clinic were treated with the hybrid approach, statistical analysis revealed no difference in the readmission rate between the two groups (OE: n = 0 vs. HMIE: n = 3, $p = 0.227$). The surgical outcomes are displayed in Table 7 (Appendices).

The conversion rate was 15%. In three patients, the laparoscopic operation was converted to laparotomy. In the first patient, an accessory left hepatic artery could not be safely preserved during division of the gastrohepatic ligament. For that reason, we decided to convert the operation in order to achieve safe dissection. The second patient was obese with BMI of 37 kg/m^2. Division in the gastrosplenic ligament and dissection of the short gastric arteries could not be conducted with safety. Furthermore, as a result of obesity, the right and left crura could not be visualized. Consequently, the surgery was converted to open esophagectomy. In the third patient, an unclear structure was seen in the lesser curvature during laparoscopy. A gastric tumor could not be excluded. We converted the operation to evaluate the structure, and frozen section biopsy was performed. Since histopathological analysis revealed no malignancy, we performed open Ivor Lewis esophagectomy.

4.4 Oncological Outcomes

The two approaches demonstrated equivalent oncological outcomes (Table 7, Appendices). The median number of harvested LN was not statistically different between the two groups (OE: 18 vs. HMIE: 16, $p = 0.333$). The majority of patients were staged as R0 (94.1%) and two patients (5.9%) as R1 (OE: n = 1 vs. HMIE: n = 1). There were not R2 resections. Neoadjuvant treatment was not conducted in both patients with positive resection margins. The patient in the HMIE group was diagnosed with advanced esophageal cancer with obstruction of esophagus and inability of oral and fluid intake. Gastroenterological treatment with stent implantation was not feasible because of increased tumor volume; consequently, primary surgical resection was performed with palliative intent. The second patient in the OE group rejected neoadjuvant treatment for histologically diagnosed esophageal adenocarcinoma (uT2, uN+) and underwent primary surgery. Histological examinations revealed positive radial margins in both patients, whereas the distal margins were negative.

Moreover, we conducted statistical analysis to compare the histological resection margins between neoadjuvant treated and no neoadjuvant treated patients. Rates of R0 resection were statistically higher in neoadjuvant treated patients ($p = 0.05$). In 25% of no neoadjuvant treated patients, positive resection margins were revealed in histological analysis (Table 8, Appendices).

4.5 Postoperative Morbidity

Initially was calculated the overall incidence of complications, which was defined as the number of patients who experienced at least one postoperative complication (surgical, gastroenterological, pulmonary, or secondary) divided by the total number of patients. No significant difference was found in the overall incidence of complications between the two groups ($p = 1.000$).

We examined the postoperative surgical and gastroenterological complications according to the ECCG guidelines. Surgical and gastroenterological complications occurred in 17.6% of the patients. Two patients in the OE group and four patients in the HMIE group developed at least one surgical complication ($p = 0.656$). Of note, a single patient may have had more than one complication. The incidence of complications was calculated as the number of patients who experienced at least one surgical/gastroenterological complication divided by the total number of participants in the group. Surgical and gastroenterological complications are displayed in Table 9 (Appendices).

We observed no difference in the rate of anastomotic leakage between the OE and HMIE group (OE: n = 1 vs. HMIE: n = 1, $p = 1.000$). Anastomotic stricture requiring reintervention was presented in one patient in the HMIE group. Conduit necrosis was not reported in our series. One patient was diagnosed with DGE postoperatively, which was treated with pyloric balloon dilatation and intramuscular quadrant injection of Botulinum toxin. Two patients developed thoracic wound infection, whereas thoracic or abdominal wall dehiscence was not reported.

Postoperative diaphragmatic hernia was seen in one patient following hybrid esophagectomy, which was treated surgically during hospital stay. Statistically significant differences in the remaining surgical and gastroenterological complications were not found.

We examined the rate of pulmonary complications according to the ECCG standardized list for recording complications associated with esophagectomies (Table 10, Appendices). Incidence of pulmonary complications was 23.5% in the OE group and 41.1% in the HMIE group ($p = 0.465$). Pneumonia was diagnosed in eight patients postoperatively, without significant differences between the two groups (OE: 17.6% vs. HMIE: 29.4%, $p = 0.688$). Following hybrid esophagectomy, four patients developed pleural effusion, which required tube drainage (OE: 5.9% vs. HMIE: 23.5%, $p = 0.335$). Pneumothorax was developed only in patients who underwent the hybrid procedure; however, statistical analysis revealed no significant difference (OE: 0 vs. HMIE: 23.5%, $p = 0.103$). Three patients in the HMIE group developed respiratory insufficiency requiring reintubation and mechanical ventilation. Cause of the respiratory insufficiency was pneumonia in all patients. None of the patients experienced tracheobronchial injury, ARDS, or pulmonary edema.

Eight reoperations and nine reinterventions were conducted postoperatively (Table 11). Statistically significant differences in reoperation and reintervention rate were not found between HMIE and OE approach (Table 12, Appendices). In the OE group, none of the patients underwent reoperation.

Five out of eight reoperations were performed in one patient who underwent HMIE. This patient was a 63 years old woman with medical history of Crohn's disease. The patient was diagnosed with SCC in middle esophagus during follow-up EGD for Crohn's disease. Following five cycles of neoadjuvant chemoradiotherapy, the patient underwent HMIE. On day thirteen post-surgery, the patient developed acute dyspnoe, and the laboratory examination showed increased white blood cells (WBC). The chest X-ray examination revealed herniation of small intestine into thorax (Figure 11). Consequently, we performed emergency laparotomy with reduction of the diaphragmatic hernia and closure of the hiatal defect. Furthermore, during hospital stay, the patient presented chylothorax, which was treated initially with parenteral nutrition, no enteral intake, and administration of octreotide. However, daily chylothorax output was not reduced. The patient was hypovolemic due to output of more than 1 litre per day. Since conservative treatment was unsuccessful, we conducted open laparotomy with ligation of the thoracic duct. The thoracic duct was dissected between two overholts and closed with nonabsorbable suture. The last complication was an infected thoracic wound, which was treated with VAC therapy. Wound debridement and VAC therapy were conducted three times in operating theater. Ten days after the first VAC operation, the VAC-System was removed, and the wound was closed with suture material. The patient was discharged on day 53. Although the postoperative course was complicated, the histological outcome showed pathologic complete response (T0, N0)

The remaining three reoperations in the HMIE group were performed because of infected thoracic wound and pleural empyema. Specifically, on postoperative day nine, the patient with infected thoracic wound was put on VAC therapy. Five days after initiation of the VAC therapy, the VAC-System was removed, and the wound was closed with suture material. The patient was discharged on day 18.

Figure 10: Chest X-ray examination was conducted in a patient with dyspnoe and elevated WBC on day thirteen post surgery. The chest X-ray showed extensive herniation of small intestine into thorax.

The third patient in the HMIE group underwent reoperation because of pleural empyema. The patient developed initially an anastomotic leak type II, which was treated with stenting. A reintervention was performed because of stent dislocation during hospital stay. Three days after discharge, the patient was readmitted because of hematemesis and hemorrhagic shock, requiring immediate EGD. Acute bleeding in the area of anastomosis was managed with endoscopic application of hemostatic powders and clips. The dislocated stent was removed, and a new one was placed. Furthermore, pleural empyema was demonstrated in the contrast-enhanced CT. Through right thoracotomy, empyema was removed, debridement was performed, and two chest drains were placed. During hospital stay, the stent was removed without evidence of anastomotic leak. The patient spent seven days in the ICU and left the hospital after 24 days. Follow-up examinations revealed no persistent anastomotic leakage.

Nine reinterventions were conducted postoperatively. Statistical analysis revealed no significant differences between the open and minimally invasive procedure ($p = 0.597$). Two reinterventions were performed in the OE group and seven in the HMIE group.

The first patient in the HMIE group was a male aged 40 years with no comorbidity in medical history. The patient suffered postoperatively from dysphagia, and oral feeding was insufficient. Gastrografin swallow examination demonstrated delayed passage of contrast into duodenum. Initially, we conducted EGD with pyloric balloon dilatation; however, relief of symptomatic was not achieved. Consequently, a second EGD was performed with intramuscular quadrant injection of Botulinum toxin. The intervention was successful, the postintervention course was uneventful, and the patient was able to eat and drink without dysphagia. The patient was discharged from the hospital on postoperative day 21.

The second patient in the HMIE group underwent five reinterventions during hospital stay. The patient was described above since he was reoperated for pleural empyema. The patient underwent EGD with stent implantation because of anastomotic leak. The second intervention was conducted because of stent dislocation. We conducted the third EGD to manage acute anastomotic bleeding and to replace the migrated stent. Finally, the stent was removed during the fourth EGD without evidence of persistent anastomotic leak. The fifth intervention was chest drain placement because of pneumothorax.

In the OE group, one patient required intervention postoperatively. The patient was a 59 years old man without preexisting medical history. Preoperative staging showed uT4 uN+ tumor. Neoadjuvant treatment, according to FLOT protocol, was performed followed by open Ivor Lewis esophagectomy. On postoperative day 5, the contrast esophagram revealed anastomotic leak. The patient was asymptomatic without clinical evidence of sepsis. EGD was conducted, and stent was placed. The length of hospital stay was 17 days. The stent was removed 22 days after discharge. The histopathological analysis revealed T2 tumor with two positive LN.

Table 7: Reinterventions and reoperations following HMIE and OE.

Reoperations and Reinterventions			
	Complication	**Reoperation**	**Reintervention**
Reoperations in the HMIE group	Postesophagectomy diaphragmatic hernia	Laparotomy with reduction of the hernia and closure of the hiatal defect	-
	Chylothorax	Ligation of thoracic duct	-
	Infected thoracic wound	VAC therapy	-
	Pleural empyema	Thoracotomy with surgical drainage and placement of two chest drains	-
Reinterventions in the HMIE group	Delayed gastric emptying	-	Pyloric balloon dilatation. Intramuscular quadrant injection of Botulinum toxin.
	Anastomotic leak	-	EGD with stent
	Pneumothorax	-	Chest drain
Reinterventions in the OE group	Anastomotic leak	-	EGD with stent

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; EGD, Esophagogastroduodenoscopy; VAC, Vacuum Assisted Closure therapy)

According to the ECCG guidelines, cardiac, urologic, thromboembolic, neurological complications, and infections following esophagectomy were included in our study (Table 13, Appendices). The rate of cardiac complications was similar between the two groups. Following esophagectomy, 14.7% of the patients developed new-onset atrial fibrillation. Myocardial infarction, acute heart failure, and ventricular arrhythmia were not observed postoperatively.

Thromboembolic complications occurred in 5.9% of the patients in the OE group. None of the 17 HMIE patients experienced a thromboembolic complication. Interestingly, only patients in the hybrid group developed postoperative delirium, which was treated in all cases with environmental, supportive, and pharmacologic interventions. This difference was statistically significant (OE: 0 vs. HMIE: 29.4%, $p = 0.044$). Multiple organ dysfunction syndrome was not reported in our patients.

In our series, 55% of the patients did not develop a postoperative surgical complication and were classified as Clavien-Dindo grade 0/I. Patients with postoperative complications were identified as having the following grades of disease: grade II; n = 5 (15%), grade III; n = 6 (18%), grade IV; n = 4 (12%) (Table 15). The mortality rate was zero in our series (Figure 12, Appendices).

Six patients with postoperative complications were classified as Clavien-Dindo grade III (OE: n = 2 vs. HMIE: n = 4, $p = 0.656$). Three patients were treated surgically, whereas two patients underwent endoscopic treatment (EGD with stent implantation) for anastomotic leak. In one patient, chest drainage was placed under local anesthesia.

Life-threatening complications requiring ICU-management were observed in four patients. One patient with hemorrhagic shock and three patients with respiratory insufficiency were classified as Clavien-Dindo grade IV complications. The three patients with pneumonia and respiratory insufficiency were reintubated in our ICU department, whereas the patient with hemorrhagic shock underwent immediate EGD for anastomotic bleeding. Multiorgan dysfunction was not reported in our series. Although grade IV complications were developed in patients treated with the hybrid procedure, statistical analysis revealed no significant difference in the incidence of grade IV complications between the two groups ($p = 0.103$).

Table 8: Postoperative surgical complications according to Clavien-Dindo classification.

Clavien-Dindo Classification					
Grade	**Overall collective (n = 34)**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**	**OR (95% CI)**
Grade 0/I (n, %)	19 (55.9%)	11 (64.7%)	8 (47.1%)	0.491	0.485 (0.122 – 1.922)
Grade II (n, %)	5 (14.7%)	4 (23.5%)	1 (5.9%)	0.335	0.203 (0.02 – 2.047)
Grade III (n, %)	6 (17.6%)	2 (11.8%)	4 (23.5%)	0.656	2.308 (0.362 – 14.717)
Grade IV (n, %)	4 (11.8%)	0	4 (23.5%)	0.103	-
Grade V (n, %)	-	-	-	-	-

The majority of patients experienced an uncomplicated postoperative course. Mortality rate was zero. The Fisher's exact test was utilized. P-values are 2-sided.

4.6 Predictive Factors of Pulmonary Complications

The majority of postoperative complications affect the respiratory system. We conducted univariate and multivariate logistic regression analysis to assess clinically relevant predictive factors for the development of pulmonary complications. Age, gender, BMI, neoadjuvant treatment, pulmonary comorbidity, cardiac comorbidity, and type of surgical procedure (HMIE or OE) were analyzed as potential predictive factors (Table 14). According to the study by

Raymond et al. with a total of 4,321 participants, BMI of more than 35 kg/m^2 and age older than 65 years were significant predictors of postoperative morbidity and mortality (RAYMOND et al., 2016). For that reason, the same values were evaluated in our series.

Univariate analysis revealed that BMI more than 35 kg/m^2 is a risk factor for the development of postoperative respiratory complications (25.8% vs. 100%, $p = 0.03$). Furthermore, univariate analysis showed statistically increased risk for respiratory complications in patients with preexisting pulmonary diseases (22.2% vs. 71.4%, $p = 0.02$). Specifically, 80% of patients with COPD and 50% of patients with asthma developed postoperative pulmonary complications. On the other hand, respiratory complications were observed in 22.2% of the patients without history of pulmonary comorbidity. All other variables, including age, gender, cardiac comorbidity, neoadjuvant chemoradiation, and surgical procedure, were not detected as predictive factors.

The multivariate logistic regression analysis did not confirm BMI as independent risk factor for the development of respiratory complications (OR = 1.09, CI = 0.1-9.7, $p = 0.94$). Furthermore, patients with preexisting respiratory disease were not at higher risk for postoperative pulmonary complications (OR = 3.29, CI = 0.4-24.8, $p = 0.25$). In accordance with the results of the univariate analysis, the multivariate analysis revealed that surgical procedure is not a risk factor for the development of pulmonary complications.

Table 9: Uni- and multivariate analysis of predictive factors for pulmonary complications after esophagectomy.

Uni- and multivariate analysis of predictive factors for pulmonary complications					
	Univariate analysis		**Multivariate analysis**		
Predictive factors	**Pulmonary complications**	**p value**	**OR**	**CI**	**p value**
Age (≤65/>65 years)	30.4%/36.4%	1.00	0.27	0-5	0.38
BMI (≤35/>35 kg/m^2)	25.8%/100%	0.03	1.09	0.1-9.7	0.94
Gender (male/female)	33.3%/28.6%	1.00	1.03	0.1-15.5	0.98
Cardiac Comorbidity	26.9%/50%	0.39	106857690.36	0-Inf.	0.99
Pulmonary Comorbidity	22.2%/71.4%	0.02	3.29	0.4-24.8	0.25
Neoadjuvant treatment	25%/34.6%	1.00	4.15	0.2-89.1	0.36
Surgical procedure (HMIE/OE)	41.2%/23.5%	0.46	0.17	0-1.5	0.11

Fisher's exact test was utilized for the univariate analysis. Multivariate analysis consists of a multiple logistic regression model. Results are presented as OR, 95% CI, and p-values.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; OR, odds ratio; CI, confidence interval; BMI, body mass index; Inf., Infinity)

5 Discussion

OE is associated with increased rate of postoperative complications, making it one of the procedures with the highest impact on patients' quality of life. Postoperative complications have been linked to increased mortality, longer hospital stay, increased readmission rate, decreased quality of life, and decreased survival. For that reason, MIE was developed with the aim to reduce postoperative morbidity without compromising on oncological safety. The advantages of laparoscopic procedures could be utilized in hybrid esophagectomies, reducing the esophagectomy related complications. Hybrid technique was introduced in 2016 as a surgical approach for EC in the Clinic of General, Visceral, Vascular, and Pediatric Surgery in Homburg/Saar, in Germany.

In our institution, several procedures, including anti-reflux operations, gastrectomies, bariatric procedures, hepatic resections, colorectal surgeries, are performed though minimally invasive approaches. Laparoscopic procedures are associated with less blood loss, controlled pain, reduced stay in ICU, decreased pulmonary complications, shorter length of hospital stay, and better quality of life compared to open procedures (BUIA et al., 2015; LI et al., 2016). Our experience with laparoscopic procedures combined with our effort to reduced postoperative complications associated with esophagectomies have grown our interest to introduce a minimally invasive procedure, which could improve the postoperative outcomes. Our interest in hybrid esophagectomy was developed after an internship in the University Clinic of General Surgery in Freiburg, where minimally invasive esophagectomy is conducted as hybrid procedure with laparoscopy and thoracotomy.

HMIE includes advantages of laparoscopy, such as decreased inflammatory response to surgical trauma, reduced muscular stress, and lower albumin and fluids loss. Reduction of inflammatory factors such as interleukin, procalcitonin, liver enzyme, and lactate levels could be associated with decrease in postoperative complications, such as pneumonia, sepsis, and wound infection. However, although several studies have been evaluated the role of HMIE, superiority of HMIE over OE is controversial. For that reason, the german S3 guidelines do not recommend hybrid or total minimally invasive esophagectomies as standard procedures for the treatment of EC. We conducted this survey to evaluate the results of the first 17 HMIEs and to compare HMIE with OE.

Thirty-four patients were included in the study. Patients in the HMIE group were matched with 17 patients in the OE group using a 1:1 ratio and the nearest-neighbour score matching. Propensity score matching method was utilized to reduce selection bias by creating two groups with similar preoperative characteristics. Propensity scores were generated using the covariates of age, BMI, pulmonary comorbidity, cardiac comorbidity, histologic tumor type, and neoadjuvant treatment. Both groups were well balanced for the variables age, BMI, pulmonary comorbidities, cardiac comorbidities, histologic type, pTNM, and neoadjuvant treatment. Statistically significant differences were not found in the baseline characteristics between the two groups. The OE and HMIE groups were homogeneous in terms of patient- and tumor-related data.

5.1 Surgical and Oncological Outcomes

Although learning curve was included in our study, operative time was not significantly longer in the HMIE group. The introduction of the laparoscopic approach was not associated with prolonged operative time. Similar results were observed in retrospective, prospective studies, and randomized trials (BAILEY et al., 2013; HAMOUDA et al., 2010; MARIETTE et al., 2019; YUN et al., 2017). The MIRO trial reported comparable operative time between OE and HMIE, whereas longer operative time was seen in the TMIE group in the TIME trial, where TMIE was compared with OE (MARIETTE et al., 2019; STRAATMAN et al., 2017).

Patients in the HMIE group spent more days in the ICU/IMCU; however, this difference was not associated with prolonged hospital stay compared to the OE group. The median stay in our ICU/IMCU was 5 days in the HMIE group. Since ICU and IMCU are located in the same department, stay in the ICU or in the IMCU cannot be differentiated. The difference in the ICU/IMCU stay between the two methods is attributed to two patients in the HMIE group, who experienced a complicated postoperative course with pneumonia and respiratory insufficiency. The length of stay in ICU/IMCU was more than 25 days for both patients.

Results comparing hospital stay between open and minimally invasive procedures are conflicting in the literature. Several retrospective studies and the MIRO trial reported no difference in hospital stay between OE and HMIE (BRIEZ et al., 2012; HAMOUDA et al., 2010; HOEPPNER et al., 2014; MARIETTE et al., 2019). However, other surveys documented shorted hospital stay in the HMIE group (GLATZ et al., 2017; YUN et al., 2017). The prospective nonrandomized study by Bjelovic et al. with a total of 88 patients, although showed shorted ICU stay in favor of the HMIE group, reported similar length of hospital stay between OE and HMIE (BJELOVIC et al., 2016).

Controversial issue is the oncologic efficacy of the MIE. In our study, the median number of retrieved LN was 16 in the HMIE group and 18 in the OE group ($p = 0.333$). These results are similar to the outcomes published by other studies. In a meta-analysis, which included 16 studies with 1,212 patients, the median number of dissected LN was 16 following MIE (DANTOC et al., 2012). Sihag et al. and Hamouda et al. reported a median number of 19 and 13 LN, respectively (HAMOUDA et al., 2010; SIHAG et al., 2012). Controversy exists between the guidelines regarding the extent of lymph node dissection. According to the AJCC recommendations, the minimum number of LN that should be retrieved is 10, in the German S3 guidelines 20, and in the National Comprehensive Cancer Network (NCCN) guidelines 15 LN. Excluding the recommendations of the German guidelines, the number of the retrieved LN in our study was oncologically sufficient.

In agreement with results of other authors, we found that radical resection and number of retrieved LN were comparable between the groups (HAMOUDA et al., 2010; MARIETTE et al., 2019). In the majority of patients, R0 resection was achieved, whereas only two patients with advanced disease underwent R1 resection (OE: n = 1 vs. HMIE: n = 1). Other studies reported increased rates of R1 resection compared to our results. In a prospective survey, positive resection margins were observed in 27.3% of the patients in the HMIE group (BJELOVIC et al., 2016).

According to our findings, neoadjuvant treated patients had statistically increased rates of R0 resection compared to no neoadjuvant treated patients. This result is in accordance with a recent RCT that reported statistically higher R0 resection rates, prolonged disease-free interval, and better overall survival in patients who underwent radiochemotherapy followed by surgery compared to surgery alone (YANG et al., 2018). Radiochemotherapy is associated with shrinkage of the primary tumor leading to increased R0 resection rates.

5.2 Postoperative Complications

Effectiveness of HMIE in reducing respiratory and overall morbidity is controversial. To the best of our knowledge, few studies have compared OE with HMIE. In our series, the incidence of surgical, gastroenterological, and pulmonary complications was similar between the two approaches. Our hypothesis that laparoscopic approach could reduce the incidence of postoperative morbidity was not confirmed.

MIE is not recommended as standard procedure in the treatment of EC in the German guidelines, since the number of RCTs is limited and the outcomes of retrospective, prospective studies, and meta-analyses are controversial. Results regarding operative time, blood loss, postoperative complications, and length of hospital stay are inconsistent between studies. Although the aim of MIE is the reduction of pulmonary complications associated with OE, many studies failed to provide evidence supporting this assumption. In our series, the introduction of laparoscopic hybrid esophagectomy was not associated with reduction in pulmonary complications.

A multi-institutional study from the UK failed to demonstrate superiority of TMIE and HMIE over OE in terms of postoperative morbidity including pulmonary complications (MAMIDANNA et al., 2012). Postoperative morbidity and 30-day mortality were comparable between open and minimally invasive procedures. However, increased rate of postoperative reinterventions was observed in the MIE group. On the contrary, a French nationwide study, which enrolled more than 3,000 patients over a 2.5-year period, demonstrated significantly reduced mortality by 40% in the HMIE group compared to OE (MESSAGER et al., 2015).

The MIRO trial is the first prospective multicentre randomised trial that compared HMIE with OE (MARIETTE et al., 2019). According to this survey, 64% and 36% of the patients developed major postoperative morbidity in the OE and HMIE group, respectively ($p < 0.001$). Furthermore, the risk of pulmonary complications was 50% lower in the HMIE group compared to the OE group. After a follow-up of at least three years, there was a trend in the HMIE group towards improved overall and disease-free survival.

The second multicentre randomized trial was conducted between 2009 and 2011, comparing TMIE with OE (STRAATMAN et al., 2017). The incidence of postoperative complications was significantly reduced in the minimally invasive group. Postoperatively, only 12% of patients in the TMIE group were diagnosed with pulmonary infection, whereas the percentage in the OE group was 34%. However, 44% of the patients in the TMIE group were diagnosed and treated for symptomatic stenosis of the anastomosis. In addition, mortality during the first year was 32% in the MIE group compared to 23% in the OE group.

Comparable outcomes in anastomotic leak and respiratory complications were documented in a meta-analysis (SGOURAKIS et al., 2010). Reduction in postoperative respiratory complications following HMIE was not found. This result is consistent with a prospective nonrandomized cohort study that compared open with hybrid Ivor Lewis esophagectomy (BJELOVIC et al., 2016). Pulmonary complications, 30-day mortality, and length of hospital stay were comparable in both groups.

Retrospective studies have been conducted, comparing HMIE with OE. A study with a total of 153 participants revealed similar incidence of postoperative complications between the two methods (YUN et al., 2017). These findings are in accordance with a retrospective study that included 446 patients. Authors reported similar rate in short-term oncological outcomes and postoperative complications. The reported morbidity was 61-65% in both groups (SMITHERS et al., 2007).

Aim of the HMIE in our clinic was the reduction of postoperative morbidity. Since the main advantage of the laparoscopic approach is the reduced invasiveness due to minimization of the trauma, we assumed that there would be reduced inflammatory response with subsequent reduced rates of postoperative complications. However, the results of our study showed no relation between laparoscopic procedure and incidence of postoperative and pulmonary complications. Univariate and multivariate analysis revealed that BMI of more than 35 kg/m^2 and preexisting pulmonary conditions are independent risk factors for the development of postoperative respiratory complications. On the other hand, the hybrid procedure had no impact on the incidence of pulmonary complications.

This finding is in accord with studies that demonstrated no relation between minimally invasive procedures and incidence of complications. Specifically, a retrospective study by Shiraishi et al. evaluated the postoperative outcomes after TMIE with thoracoscopy. Significant reduction in pulmonary complications following thoracoscopy was not found (SHIRAISHI et al., 2006). A prospective study by Hamouda and colleagues recruited 75 patients comparing open, hybrid, and total minimally invasive esophagectomy (HAMOUDA et al., 2010). Similar to our survey, length of hospital stay, postoperative morbidity, and mortality rates were similar between OE and MIE.

Postoperative complications developed in 45% of our patients. A retrospective study, which was conducted in Freiburg, reported at least one complication in more than 50% of the patients. Although in-hospital and 30-day mortality was zero in our series, other studies reported mortality rates of 0.8-2% following HMIE (BJELOVIC et al., 2016; GLATZ et al., 2017; MARIETTE et al., 2019; WOODARD et al., 2016). As causes of mortality have been described mediastinitis and septic shock, necrosis of gastric tube, respiratory failure, chylothorax, and hemorrhagic shock. Gastric conduit necrosis was not observed in our patients, whereas other studies have reported an incidence of 2-5% after HMIE (GLATZ et al., 2017; MARIETTE et al., 2019). Furthermore, none of our patients developed ARDS. In contrast, in other studies, the estimated incidence of ARDS is 2-6.7% (BJELOVIC et al., 2016; WOODARD et al., 2016).

Postoperative complications are considered as a significant factor leading to unexpected readmissions. It has been reported that patients who develop more than one complication have 4-fold greater risk for readmission. Kelly et al. conducted a retrospective study evaluating a total of 42,609 patients from the 2011 American College of Surgeons National Surgical Quality

Improvement Program database. The readmission rate after esophagectomy or gastrectomy was 13.5% (KELLY et al., 2014). In our institution, the overall readmission rate was 8.8%.

Although more reoperations and reinterventions were conducted in the HMIE group, statistical differences were not found. Five out of eight reoperations in the HMIE group were conducted in one patient with Crohn’s disease. Half of all reoperations in this group were wound revisions with VAC-therapy in the operating theater. Intrathoracic or intraabdominal reoperations were conducted in cases of pleural empyema, chylothorax, and hiatal hernia. Regarding reinterventions, two out of seven procedures in the HMIE group were conducted because of stent dislocation.

In a survey by Woodard and colleagues in the University of California in San Francisco, the reoperation rate in the HMIE group was 4.6% in a total of 131 patients. However, authors mentioned that most reoperations occurred in the first half of their experience with the hybrid technique (WOODARD et al., 2016). In our retrospective study, reoperations were conducted only in the HMIE group. We present the results of our first cases with the new technique. Since the learning curve process was included, further reduction in reoperation rate is expected in the next cases.

Anastomotic leakage is a postoperative complication with a reported incidence of 2.5-10.2% (LUKETICH et al., 2012; MARKAR et al., 2015; VAN DAELE et al., 2016; WOODARD et al., 2016). Anastomotic leak is associated with prolonged hospitalisation, reduced quality of life, and increased mortality rates. In the hybrid procedure, anastomosis is not conducted thoracoscopically. Adopting the laparoscopic approach, the technically demanding and high-risk thoracoscopic anastomosis is avoided.

RCTs showed no significant difference in the incidence of anastomotic leakage between open and HMIE or TMIE (MARIETTE et al., 2019; STRAATMAN et al., 2017). This outcome is in accordance with retrospective studies that reported similar rates of anastomotic leak between the two approaches (BRIEZ et al., 2012; GLATZ et al., 2017; YUN et al., 2017). In agreement with these findings, our results showed equivalence in the incidence of anastomotic leakage between OE and HMIE. In our series, anastomotic leak was observed in two patients (OE: n = 1 vs. HMIE: n = 1). These patients were treated with stent implantation. Although the majority of studies showed results similar to our findings, anastomotic leak incidence more than 10% following HMIE has been reported (HAMOUDA et al., 2010).

The reported incidence of DGE in the literature is estimated at 10-50% (AKKERMAN et al., 2014). DGE is attributed to bilateral vagotomy that results in gastric dysmotility and pyloric denervation. Removal of the gastric pacemaker neurons located to the lesser curve is also a causative factor. DGE is associated with increased postoperative morbidity and prolonged hospitalization. In our series, Heineke-Mikulicz pyloroplasty or pyloromyotomy were not conducted, since are associated with long-term complications such as bile reflux and dumping syndrome, whereas statistically significant reduction in the rate of DGE is not reported (AKKERMAN et al., 2014; BENEDIX et al., 2017; ZHANG et al., 2017).

In our institution, treatment of DGE included diet restrictions and administration of prokinetic agents. When conservative treatment had failed to resolve symptomatic, endoscopic intervention with balloon dilatation or injection of Botulinum toxin was performed. Surgical treatment for DGE was not performed in our patients. Furthermore, redundant conduit was not presented in our patients.

Benedix et al. conducted a prospective study including 182 patients who underwent transthoracic esophagectomy (BENEDIX et al., 2017). DGE was observed in 26.1% of the patients. Although the majority of cases responded to conservative treatment, intervention was required in 38% of the patients. Zhang et al. reported that 18.2% of the patients were diagnosed with DGE, and prokinetic treatment was successful in 75% of cases (ZHANG et al., 2017). One patient was diagnosed with DGE in our study. Statistically significant difference in the incidence of DGE between HMIE and OE was not found. The reported incidence of 3% in our series is less compared to results published in previous studies. In a retrospective study in Freiburg, the rate of DGE following HMIE was 23% and statistically increased compared to OE (GLATZ et al., 2017).

Diaphragmatic herniation constitutes a postoperative complication of esophagectomy with a reported incidence of 0.5-15% (ARGENTI et al., 2016; GANESHAN et al., 2013). Main cause is considered the extensive dissection of hiatus to achieve visualization and mobilization of esophagus, with subsequent progressive widening caused by increased intraabdominal pressure and negative intrathoracic pressure (OOR et al., 2016). Incidence of herniation after MIE is inconsistent with rates between 2% and 26% (BRONSON et al., 2014). Although some studies reported increased rates of postoperative herniation in patients who underwent minimally invasive procedures (BENJAMIN et al., 2015; GOOSZEN et al., 2018; OOR et al., 2016), others failed to demonstrate statistically significant differences between the two approaches (GANESHAN et al., 2013). It is assumed that paucity of adhesions after MIE, which might prevent herniation, as well as the need to widen hiatus more extensively during laparoscopy can increase the incidence of herniation.

Retrospective studies reported 8% incidence of herniation after minimally invasive transhiatal and McKeown esophagectomy and 5% following hybrid Ivor Lewis procedure (BRONSON et al., 2014; GLATZ et al., 2017). In our institution, one patient (5.9%) was diagnosed with hiatal hernia postoperatively. Statistical analysis showed no difference between open and HMIE. After two cases of postoperative hernia, we no longer perform extended division of diaphragm. Appropriate visualization and mobilization of distal esophagus is achieved with minimal phrenotomy.

The reported incidence of chylothorax after esophagectomy is estimated at 0.4-4% (CRUCITTI et al., 2016; MIAO et al., 2015). Thoracic duct transports up to 4 litres of chyle daily, which contains proteins, lipids, fat-soluble vitamins, immunoglobulins, and lymphocytes. An intraoperative injury of thoracic duct can cause persistent chyle loss, which results in hypovolemia, hypoalbuminemia, malnutrition, and immunosuppression. Reduction in lymphocyte count is associated with postoperative complications and infections (CRUCITTI et al., 2016).

In our series preventive ligation of thoracic duct was not conducted, since several studies failed to demonstrate reduction in postoperative chylothorax following prophylactic ligation (HOU et al., 2014; LEI et al., 2018). Chyle leak was observed only in one patient in our analysis (2.9%). The patient was treated conservatively with parenteral nutrition, no enteral intake, and octreotide. However, the treatment was not successful, and the patient underwent ligation of thoracic duct. Statistical analysis revealed no significant difference between OE and HMIE.

The number of studies that compared the incidence of postoperative chylothorax between open and hybrid Ivor Lewis procedure is limited. In a study by Woodard et al., 3.4% of the patients in the HMIE group developed postoperative chylothorax (WOODARD et al., 2016). Chylothorax in 6% of the patients who underwent HMIE was reported in a retrospective survey with 75 patients (HAMOUDA et al., 2010). Similar to our results, both studies reported no cases of chylothorax in the OE group. Authors reported that the difference between OE and HMIE was not statistically significant. However, there is a trend that in the HMIE group more patients develop chylothorax. This fact can be attributed to the laparoscopic transhiatal mobilization of the distal esophagus, which can cause injury to the thoracic duct because of limited visualization.

Cardiac complications did not differ between the two approaches. Myocardial infarction, acute heart failure, pericarditis, and ventricular dysrhythmia were not observed postoperatively. Fifteen percent of our patients presented new-onset atrial fibrillation. Incidence, more than 10%

following MIE and OE, was reported in a retrospective study by Sihag and colleagues (SIHAG et al., 2012). A study performed by Smithers et al. reported increased rates of arrhythmia after MIE compared to OE. Arrhythmia presented in 42% and 28.4% of the patients, respectively (SMITHERS et al., 2007). In our study, differences between the two procedures were not found.

Interestingly, the incidence of postoperative delirium was statistically increased in the laparoscopic group. Delirium is a possible complication after major surgical procedures and has been associated with increased costs and prolonged ICU and hospital length of stay. Unlike our results, studies have reported increased or similar rates of delirium following open esophagectomy, gastrectomy, or colectomy compared to minimally invasive approaches (DEZUBE et al., 2020; SHIN et al., 2015; TAN et al., 2015). There is a hypothesis that excessive abdominal wall trauma results in increased levels of cytokines and cortisol in the central nervous system, which impairs cognitive function. Therefore, reduced perioperative stress and inflammatory responses are thought to minimize the occurrence of delirium in minimally invasive surgeries.

In our retrospective study, differences in age, preexisting pulmonary diseases, and postoperative complications were not detected between patients with delirium and those who did not develop delirium. However, delirium was observed more frequently in patients with cardiac comorbidities ($p = 0.023$). The increased rates of delirium in the laparoscopic group were not expected, since no studies, to the best of our knowledge, reported increased rates of delirium following minimally invasive surgeries.

According to our findings, the rate of postoperative complications was similar between the two approaches. Important factor for the adoption and utilization of a new developed surgical procedure is the cost-effectiveness. As health care budgets are becoming increasingly constrained, the cost-effectiveness of new medical procedures should be established before widespread adoption. In a cost-decision analysis, MIE was estimated to cost 1641$ less than open esophagectomy (LEE et al., 2013). Consequently, MIE is cost-effective compared to OE and can be adopted as procedure of choice in the treatment of EC.

5.3 Limitations of the Study

Our study has limitations since the retrospective design and selection bias allow only limited definitive conclusions. Patients were not randomized to the surgical technique. Specifically, the HMIE has been conducted since 2016 in our department. During this period, the open procedure was performed in patients with contraindications to laparoscopic surgery and based on the preference of the surgeon.

Furthermore, although the baseline characteristics were similar between the two groups, the limited number of participants did not allow 100% matching for all parameters. Propensity score matching was used to remove bias. To some extent, hidden bias is inevitable, since additional parameters, which may influence the results, were not taken into account. However, the study design and propensity score minimize bias attributed to retrospective studies and provide safe evidence regarding the role of HMIE in the treatment of EC.

In addition, the fact that learning curve is included in our study may affect the results in favour of OE. Further follow-up is required to compare long-term outcomes and survival between open and hybrid esophagectomy.

5.4 Conclusions

Our study presents the results of the first 17 HMIEs that performed in our institution. Selection bias is eliminated by choosing those patients, but it also integrates the learning curve into the outcome. Therefore, it is likely that surgical parameters such as operative time, conversion rate, and postoperative morbidity will be further improved. Consequently, differences between the groups can be enhanced in favour of HMIE.

According to our findings, surgical outcomes of HMIE are not inferior to those of OE. On the contrary, statistically significant differences in surgical, postoperative, and oncological outcomes were not found between the two approaches.

Incidence of respiratory complications was similar in the OE and HMIE group. Our hypothesis that laparoscopy would reduce the pulmonary complications was not confirmed. The assumption that laparoscopy, through minimized surgical trauma and decreased inflammatory response, could have a beneficial outcome in our patients was not proved.

One of the major concerns that have been raised regarding MIE is the limited oncological resection. In our cohort, the number of retrieved LN and the margin negative (R0) resection rates were equivalent between the two groups. The oncological outcomes were similar in both approaches. Further studies are required to evaluate the long-term oncological outcomes and survival in patients treated with HMIE.

Finally, many surgeons remain sceptical about HMIE, perceiving poor oncological outcomes and prolonged learning curve as disadvantages of this surgical approach. In this study, we showed that hybrid Ivor Lewis is safe, resulting in radical oncological resection and similar morbidity with OE. Surgeons who are proficient in OE and laparoscopic anti-reflux and gastric surgery can safely adopt the HMIE without significant learning curve associated morbidity. HMIE is considered as a safe step towards TMIE.

Disease-free interval and overall survival were not evaluated in this study. Analysis of postoperative survival remains a task for future studies after more data on the hybrid technique are accumulated.

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7 Publication / Acknowledgements

7.1 Publication

The manuscript with the results of the study was sent for publication in the Journal “Annals of Royal College of Surgeons of England”.

7.2 Acknowledgements

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8 Curriculum Vitae

Publications

2020 Transferability of Simulation-Based Training in Laparoscopic Surgeries: A Systematic Review.

Antonios E. Spiliotis, Panagiotis M. Spiliotis, and Ifaistion M. Palios Minimally Invasive Surgery

2019 Trends in pediatric cervical spine injuries in the United States in a 10- year period.

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Journal of Orthopaedic Surgery

2018 Current concepts in intradiscal percutaneous minimally invasive procedures for chronic low back pain.

Gelalis Ioannis, Gkiatas Ioannis, Spiliotis Antonios, et al. Asian Journal of Neurosurgery

9 List of Tables and Figures

9.1 List of Tables

9.2 List of Figures

10 Disclosure Statement

I, Antonios Spiliotis, declare that I wrote the submitted dissertation with the title: " Introduction of hybrid minimally invasive esophagectomy and comparison of perioperative outcomes following open versus hybrid esophagectomy; a retrospective study." independently and without illegal help of third parties. This study does not constitute a copy of other works.

Homburg, 28.11.2020

Antonios Spiliotis

11 Appendices

Table 10: Surgical and oncological outcomes following HMIE and OE for esophageal cancer

Surgical and oncological outcomes					
Outcomes	**Overall collective (n = 34)**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**	**OR (95% CI)**
Operative time (median [IQR], minutes)	296 [275 - 330]	295 [270 - 316]	297 [282 -341]	0.418	-
ICU stay (median [IQR], days)	4 [2 - 7]	3 [2 - 4]	5 [4 - 7]	0.028	-
Hospital stay (median [IQR], days)	15 [14 - 18]	15 [14 - 17]	16 [14 - 22]	0.425	-
In-hospital mortality, n	0	0	0	-	-
Intraoperative Transfusion (n [range], units)	6 [0 - 4]	6 [0 - 4]	0	0.485	0 (0 - 5.27)
Postoperative Transfusion (n [range], units)	8 [0 - 4]	3 [0 - 2]	5 [0 - 4]	0.688	1.91 (0.3 - 14.9)
Readmission in hospital (n, [range])	3 [0 - 1]	0	3 [0 - 1]	0.227	-
Readmission in ICU (n, [range])	2 [0 - 3]	0	2 [0 - 3]	0.485	-
Harvested LN (median, [IQR])	17 [13 - 25]	18 [16 - 25]	16 [13 - 19]	0.333	-
Positive LN (median, [IQR])	0 [0 - 1]	0 [0 - 2]	0 [0 - 0]	0.318	-
Resection margin					
R0 (n, %)	32 (94.1%)	16 (94.1%)	16 (94.1%)	1.000	1 (0.01 - 83.29)
R1 (n, %)	2 (5.9%)	1 (5.9%)	1 (5.9%)	1.000	1 (0.01 - 83.29)

Quantitative variables are presented as median and IQR, and qualitative variables as absolute numbers, range, and percentages. The Fisher's exact test and two-sample Wilcoxon rank-sum test were utilized. P-values are 2-sided. Readmission ICU: two patients were readmitted in the ICU during hospital stay. The first patient was readmitted two times and the second three times in the ICU. Readmission in hospital: three patients were readmitted in our department after discharge. None of the patients was readmitted more than one time in our clinic after initial discharge. Blood transfusion: n = the number of units per treatment group, range = the number of units per patient.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; CI, confidence interval; OR, odds ratio; ICU, intensive care unit; IQR, interquartile ranges; LN, lymph nodes)

Table 11: Resection margins in neoadjuvant and no neoadjuvant treated patients.

Resection margins after chemotherapy				
Outcomes	**Overall collective (n = 34)**	**Neoadjuvant Chemoradiation (n = 26)**	**No neoadjuvant treatment (n = 8)**	**p value**
Resection margins (n, %)				0.05
R0 resection	32 (94.1%)	26 (100%)	6 (75%)	
R1 resection	2 (5.9%)	0	2 (25%)	

Fisher's exact test was utilized. P-value is 2-sided.

Table 12: Surgical and gastroenterological complications.

Surgical and gastroenterological complications					
Outcomes	**Overall collective (n = 34)**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**	**OR (95% CI)**
Incidence of complications (n, %)	6 (17.6%)	2 (11.8%)	4 (23.5%)	0.656	3.02 (0.4 - 37.11)
Anastomotic leakage (n, %)	2 (5.9%)	1 (5.9%)	1 (5.9%)	1.000	1 (0.01 - 83.29)
Conduit necrosis (n, %)	0	0	0	-	-
Anastomotic stricture (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Delayed gastric emptying (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Thoracic wound infection (n, %)	2 (5.9%)	0	2 (11.8%)	0.485	-
Abdominal wound infection (n, %)	0	0	0	-	-
Thoracic / abdominal wall dehiscence (n, %)	0	0	0	-	-
Abscess (n, %)	0	0	0	-	-
Diaphragmatic hernia (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Chyle leakage (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Mediastinitis (n, %)	0	0	0	-	-
Gastrointestinal bleeding (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Recurrent nerve injury (n, %)	0	0	0	-	-
Ileus (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Clostridium difficile infection (n, %)	0	0	0	-	-
Pancreatitis (n, %)	1 (2.9%)	1 (5.9%)	0	1.000	-
Liver dysfunction (n, %)	0	0	0	-	-

Complications are defined and recorded according to the guidelines of the Esophageal Complications Consensus Group (ECCG). The results are presented as absolute numbers and percentages. The Fisher's exact test was utilized. P-values are 2-sided.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; CI, confidence interval; OR, odds ratio)

Table 13: Pulmonary complications following OE and HMIE according to the ECCG guidelines.

Pulmonary complications					
Outcomes	**Overall collective (n = 34)**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**	**OR (95% CI)**
Incidence of pulmonary complications (n, %)	11 (32.3%)	4 (23.5%)	7 (41.1%)	0.465	0.440 (0.10 – 1.93)
Pneumonia (n, %)	8 (23.5%)	3 (17.6%)	5 (29.4%)	0.688	0.514 (0.101 – 2.614)
Pleural effusion (n, %)	5 (14.7%)	1 (5.9%)	4 (23.5%)	0.335	0.203 (0.02 – 2.04)
Pleural empyema (n, %)	1 (2.9%)	0	1 (5.9%)	1.000	-
Pneumothorax (n, %)	4 (11.8%)	0	4 (23.5%)	0.103	-
Pulmonary edema (n, %)	0	0	0	-	-
Atelectasis requiring bronchoscopy (n, %)	2 (5.9%)	0	2 (11.8%)	0.485	-
Respiratory failure (n, %)	3 (8.8%)	0	3 (17.6%)	0.227	-
Tracheobronchial injury (n, %)	0	0	0	-	-
ARDS (n, %)	0	0	0	-	-

As incidence of pulmonary complications is defined the number of patients who developed at least one pulmonary complication divided by the total number of participants in the group. Some patients developed more than one pulmonary complication. The results are presented as absolute numbers and percentages. Statistically significant differences were not found between the two approaches. The Fisher's exact test was utilized. P-values are 2-sided.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval)

Table 14: Total number of reoperations and reinterventions performed postoperatively.

Reoperation and reintervention rate				
Outcomes	**Overall collective (n = 34)**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**
Reoperations (n, [range])	8 [0 - 5]	0	8 [0 - 5]	0.193
Reinterventions (n, [range])	9 [0 - 5]	2 [0 - 2]	7 [0 - 5]	0.597

In the HMIE group, eight reoperations were performed, from which five were conducted in one patient. Similarly, five out of seven reinterventions were performed in one patient. No statistically significant differences in reoperation and reintervention rate were observed between the two approaches. The results are presented as absolute numbers and range of procedures per patient. Pearson Chi-Square test was utilized. P-values are 2-sided.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy)

Table 15: Secondary outcomes according to the ECCG guidelines.

Secondary outcomes					
Outcomes	**Overall collective (n = 34)**	**OE (n = 17)**	**HMIE (n = 17)**	**p value**	**OR (95% CI)**
Cardiac complications (n, %)					
Myocardial infarction	0	0	0	-	-
Congestive heart failure	0	0	0	-	-
Atrial dysrhythmia	5 (14.7%)	2 (11.8%)	3 (17.6%)	1.000	0.62 (0.09 – 4.29)
Ventricular dysrhythmia	0	0	0	-	-
Pericarditis	0	0	0	-	-
Cardiac arrest	0	0	0	-	-
Urologic complications (n, %)					
Acute renal insufficiency	1 (2.9%)	0	1 (5.9%)	1.000	-
Urinary tract infection	1 (2.9%)	0	1 (5.9%)	1.000	-
Urinary retention	0	0	0	-	-
Thromboembolic complications (n, %)					
Deep venous thrombosis	1 (2.9%)	1 (5.9%)	0	1.000	-
Peripheral thrombophlebitis	0	0	0	-	-
Pulmonary embolism	1 (2.9%)	1 (5.9%)	0	1.000	-
Stroke	0	0	0	-	-
Acute Delirium (n, %)	5 (14.7%)	0	5 (29.4%)	0.044	-
Infections (n, %)					
Generalized sepsis	0	0	0	-	-
Other infections	0	0	0	-	-
MODS	0	0	0	-	-

The results are presented as absolute numbers and percentages. The Fisher's exact test was utilized. P-values are 2-sided.

(OE, open esophagectomy; HMIE, hybrid minimally invasive esophagectomy; OR, odds ratio; CI, confidence interval; MODS, multiple organ dysfunction syndrome)

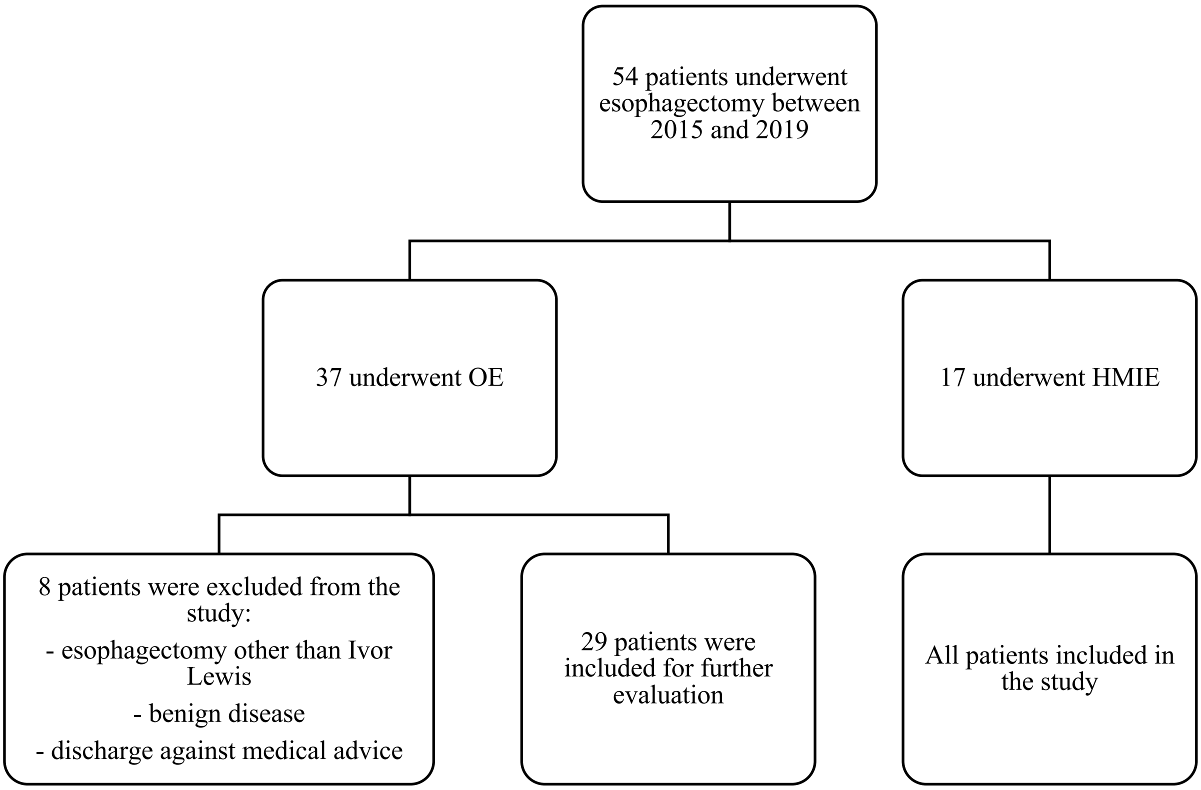

Figure 11: Patients included in survey.

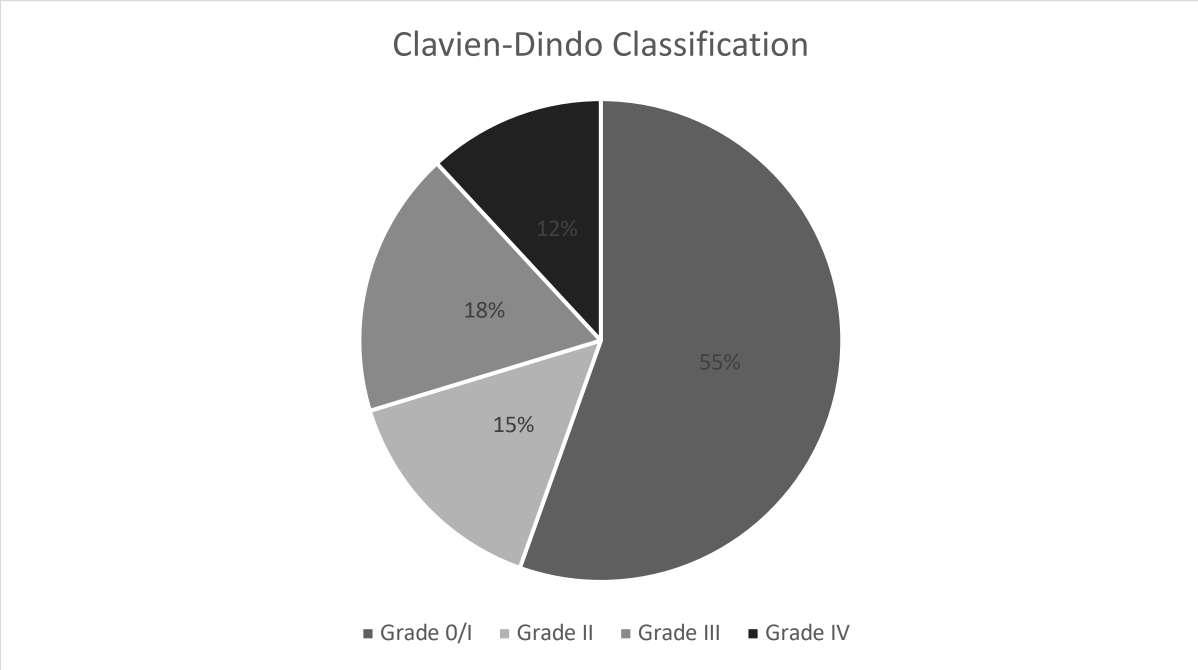

Figure 12: Clavien-Dindo classification. Postoperative complications are categorized as grade II (pharmacological treatment, blood transfusion, or parenteral nutrition is required), grade III (surgical, endoscopic, or radiological intervention is required), grade IV (life-threatening complication with single organ or multiorgan dysfunction), and grade V (death). Postoperative mortality was zero in our series. Since grade I complications are defined as any minimal deviation from the normal postoperative course without the need for extensive treatment, both no complications and grade I complications were evaluated together.