UNIVERSITY OF SZEGED FACULTY OF MEDICINE

DEPARTMENT OF SURGERY

MINIMALLY INVASIVE SURGERY FOR MOTILITY DISORDERS OF THE OESOPHAGUS

Ph.D. Thesis

LÁSZLÓ ANDRÁSI M.D.

Supervisor: György Lázár M.D., Ph.D., D.Sc.

Szeged

2021

Contents

LIST OF PAPERS

This doctoral thesis is based on the following publications:

I. Andrási, László ; Ábrahám, Szabolcs ; Simonka, Zsolt ; Paszt, Attila ; Rovó, László ; Lázár, György A Zenker-diverticulumok transcervicalis és transoralis sebészi kezelésének összehasonlító vizsgálata, rövid és hosszú távú eredmények ORVOSI HETILAP 160 : 16 pp. 629-635. , 7 p. (2019) DOI: 10.1556/650.2019.31360 IF: 0.497

II. Andrási, László ; Paszt, Attila ; Simonka, Zsolt ; Ábrahám, Szabolcs ; Rosztóczy, András ; Lázár, György Laparoscopic Surgery for Epiphrenic Esophageal Diverticulum JSLS-JOURNAL OF THE SOCIETY OF LAPAROENDOSCOPIC SURGEONS 22 : 2 Paper: 2017.00093 , 8 p. (2018) DOI: 10.4293/JSLS.2017.00093 IF: 1.654

III. Andrási, László ; Paszt, Attila ; Simonka, Zsolt ; Ábrahám, Szabolcs ; Erdős, Márton ; Rosztóczy, András ; Ollé, Georgina ; Lázár, György Surgical Treatment of Esophageal Achalasia in the Era of Minimally Invasive Surgery JSLS-JOURNAL OF THE SOCIETY OF LAPAROENDOSCOPIC SURGEONS 25 : 1 Paper: e2020.00099 , 12 p. (2021) DOI: 10.4293/JSLS.2020.00099 IF: 2.172

Total impact factor of original papers directly related to the thesis: 4.323

List of abstracts related to the subject of the thesis:

I. Andrási László, Paszt Attila, Simonka Zsolt, Ábrahám Szabolcs, Rosztóczy András1, Lázár György Laparoscopic surgery for esophageal diverticulum: short-term and long-term results 68th Congress of the Associataion of Polish Surgeons 2017. kiadványa 1401. sz. abstract, p. 491.

II. Andrási László, Paszt Attila, Simonka Zsolt, Ábrahám Szabolcs, Rovó László, Lázár György A comparative study of short and long-term outcomes for transcervical versus transoral surgery for Zenker's diverticulum 27th International Congress of th eEuropean Association for Endoscopic Surgery Sevilla, 2019. június 12-15.

III. Andrási László, Paszt Attila, Simonka Zsolt, Ábrahám Szabolcs, Rosztóczy András, Rovó László, Lázár György: Zenker's diverticulumok transcervicalis és transoralis sebészi kezelése: összehasonlító, rövid és hosszú távú eredmények A Magyar Sebész Társaság 64. Kongresszusa Debrecen, 2018. május 24-26.

IV. Andrási László, Paszt Attila, Simonka Zsolt, Ábrahám Szabolcs, Rosztóczy András1 , Rovó László11, Lázár György: Transoral and transcervical surgery for Zenker's diverticulum : short-term and lon 26th International Congress of the European Association for Endoscopic Surgery, London, 2018. május 30-június 1.

V. Andrási László: Az epiphrenalis nyelőcső diverticulumok minimálisan invazív sebészete: rövid és hosszú távú eredmények MST Sebészeti Endoszkópos Szekció XVII. Kongresszusa, Kecskemét, 2017. október 12-14.

VI. Andrási László, Paszt Attila, Simonka Zsolt, Ábrahám Szabolcs, Rosztóczy András1, Lázár György Laparoscopic surgery for esophageal diverticulum: short-term and long-term results XXI Annual Meeting of the European Society of Surgery, 2nd European Meeting of Residents and PhD Students in Surgery, Krakkó, Lengyelország, 2017. szeptember 27- 30.

Publications not directly related to the thesis:

1. Ábrahám, Szabolcs; Németh, Tibor ; Benkő, Ria ; Matuz, Mária ; Váczi, Dániel ; Tóth, Illés ; Ottlakán, Aurél ; Andrási, László ; Tajti., János ; Kovács, Viktor et al. Evaluation of the conversion rate as it relates to preoperative risk factors and surgeon experience: a retrospective study of 4013 patients undergoing elective laparoscopic cholecystectomy BMC SURGERY 21 : 1 Paper: 151 , 7 p. (2021) DOI: 10.1186/s12893-021-01152-z IF: 2.102
2. Andrási, László ; Szepes, Zoltán ; Tiszlavicz, László ; Lázár, György ; Paszt, Attila Complete laparoscopic-transhiatal removal of duplex benign oesophageal tumour: case report and review of literature BMC GASTROENTEROLOGY 21 : 1 Paper: 47 , 7 p. (2021) DOI: 10.1186/s12876-021-01625-8 IF: 3.067
3. Lorenzon, Laura ; Evrard, Serge ; Beets, Geerard ; Gonzalez-Moreno, Santiago ; Kovacs, Tibor ; D'Ugo, Domenico ; Polom, Karol ; CORSiCA, Study - EYSAC.1 Study Group (Kollaborációs szervezet) ; Andrási, László (Kollaborációs közreműködő) ; Lázár, György (Kollaborációs közreműködő) et al. Global variation in the long-term outcomes of ypT0 rectal cancers EUROPEAN JOURNAL OF SURGICAL ONCOLOGY 46 : 3 pp. 420-428. , 9 p. (2020) DOI: 10.1016/j.ejso.2019.10.010 IF: -
4. Tibor, Novák; László, Andrási ; Zsolt, Szabó ; Gábor, Németh Succesfully treated case of a patient with giant benign ovarian tumor and suicide attempt MAGYAR NŐORVOSOK LAPJA 80 : 5 pp. 231-233. , 3 p. (2017) IF: -
5. Andrasi, L ; Abraham, S ; Lazar, G A minilaparoscopos cholecystectomia mint innovativ eljaras a minimalisan invasiv hasi sebeszetben [Mini-laparoscopic cholecystectomy as an innovative method in minimally invasive abdominal surgery] MAGYAR SEBÉSZET 67 : 6 pp. 334-339. , 6 p. (2014) DOI: 10.1556/MaSeb.67.2014.6.3 IF: -
6. Petri, A; Hohn, J ; Balogh, A ; Kovach, K ; Andrasi, L ; Lazar, G Colorectalis rák májáttéteinek sebészi kezelése szinkron májreszekcióval [Surgical Treatment of Liver Metastasis in Colorectal Cancer With Simultaneous Liver Resection] MAGYAR ONKOLÓGIA 54 : 2 pp. 125-128. , 4 p. (2010) DOI: 10.1556/MOnkol.54.2010.2.6 IF: -

Cumulative impact factor: 9.492

LIST OF ABBREVIATIONS

BMI	body mass index
BTI	botulinum toxin injection
CC	Chicago classification
DES	diffuse/distal oesophageal spasm
EAT	eating assessment tool
EBD	endoscopic balloon dilatation
Endo GIA	endoscopic gastrointestinal anastomosis
FESD	flexible endoscopic septum division
GERD	gastrooesophageal reflux disease
HRM	high-resolution manometry
ISDE	International Society of Diseases of the Esophagus
LES	lower oesophageal sphincter
LHM	laparoscopic Heller myotomy
OTSC	over-the-scope clip
PEMD	primary oesophageal motility disorder
POEM	per-oral endoscopic myotomy
PPI	proton pump inhibitor
PRO	patient-reported outcome
RSI	reflux severity index
TCD	trans-cervical diverticulectomy
TSD	transoral stapler diverticulostomy

1. INTRODUCTION

As a result of the spread of minimally invasive surgery, traditional interventions, which previously caused significant surgical trauma for patients due to the opening of body cavities, were pushed into the background, while the so-called “keyhole” operative methods have disseminated rapidly due to their advantages. The trend was particularly pronounced for the three distinct oesophageal tracts, while a parallel improvement in gastroenterological diagnostics made it increasingly possible to identify patients with functional oesophageal diseases. Although they can occur in a range of age groups from young adolescents to the elderly, oesophageal motility disorders are uncommon diseases and require special testing. The use of various surgeries with the appropriate indication is only recommended for surgeons with experience in advanced oesophageal surgery and minimal invasive skills.

Primary motor disorders of the oesophagus consist of achalasia, diffuse oesophageal spasm, nutcracker oesophagus and non-specific oesophageal motility disorders. Usually, oesophageal diverticula are not stated among primary motor disorders, but, in almost every case, they are associated with a certain type of dysmotility which plays a key role in their pathogenesis.

The pharyngooesophageal or Zenker’s diverticula are pseudodiverticula of the oesophagus, containing mucosal and submucosal layers, which are typically located in the posterior wall of the hypopharynx, between the oblique fibres of the constrictor pharyngis inferior muscle and the transverse fibres of the cricopharyngeus muscle, in the so-called Killian–Laimer triangle. The lesions are considered to be pulsion type because the pharyngooesophageal intraluminal pressure increases due to the malfunction of the former muscle apparatus (spasm and insufficient relaxation). Although the exact origin of the formation of the diverticulum is still unclear, there are basically two important factors as possible causes: abnormal oesophageal motility and anatomical changes in the muscle layer of the cervical oesophageal section. The disease is quite rare, with an incidence of only 0.01–0.11% in the population; prevalence ranges from 0.06 to 4% in the US. Zenker’s diverticulum rarely occurs under the age of 30, with the majority of patients over the age of 60 (and a peak between 65 and 75 years) with a 1.5-fold male dominance (1). Symptoms can occur on a wide scale, most often dysphagia and food regurgitation, but aspiration and chronic/recurrent pneumonia are also common symptoms. Less frequently, dumplings, halitosis and odinophagia may also be present as complaints.

Epiphrenic diverticulum of the oesophagus is an outpouching of the mucosal and submucosal layers of the oesophagus which generally affects the distal third segment. Lesions are

considered to be pulsion type, as they are accompanied by dysmotility of the oesophagus in 70 to 90% of cases, known as primary oesophageal motility disorder (PEMD) (2–5). The most common motility disorders are achalasia and diffuse oesophageal spasm (DES); uncommon disorders are the so-called nutcracker oesophagus and hypertensive lower oesophageal sphincter (LES). The disease is relatively rare, with a prevalence of between 0.0015% and 2%, thus explaining the limited number of studies in the literature. It is mainly large diverticulum and diverticulum-associated functional oesophageal disorders that lead to symptoms; this is the case in up to 10 to 20% of patients (6-10). Symptoms may be variable: the most usual include dysphagia, regurgitation of food, chest pain as a consequence of the diverticulum and motor dysfunction of the oesophagus (11).

First described by Sir Thomas Willis in 1674, achalasia is a chronic motility disorder of the oesophagus characterised by a lack of peristalsis and the inability of the LES to relax (12-13). Despite being rare, it is the most common primary motor disorder of the oesophagus with an incidence of 1/100,000 and a prevalence of 10/100,000; (14) no gender predominance can be observed. It may be developed at any age, but it occurs most commonly in the third to fifth decades of life. The aetiology of achalasia is still unclear, but, ultimately, it is a selective disorder of the inhibitory neurons in the myenteric (or Auerbach's) plexus of the distal oesophagus and the LES. In most cases, clinical presentation is dominated by progressive dysphagia, regurgitation and chest/epigastric pain, with heartburn and coughing at night also typical. In gastroenterological diagnostics, functional assessments play a primary role. High-resolution manometry (HRM) is quite a new standard tool which has made it possible to distinguish three types of achalasia (15). Type I (which corresponds to the previous classic type) refers to aperistalsis of the oesophageal body and a relaxation disorder of the LES. In type II (compression), the morphology of waves in the oesophageal body is the same as that seen in type I, but the amplitudes exceed 30 mmHg. In type III (spastic), tall (>200 mmHg), wide contractions can be seen in the distal oesophagus.

Regardless of the localization of the functional oesophageal lesion, its manifestation (Zenker's diverticulum, epiphrenic diverticulum and achalasia cardiae) and the choice of surgical type, all surgical therapeutic efforts are aimed at the disruption of abnormal muscle function (myotomy) with or without secondary developed organic lesion (diverticulum) removal. Diverticula cannot be cured by conservative treatment; they gradually grow over time. In the case of motility disorders, surgical therapy is only justified in cases causing complaints, and it

is also a solution for the prevention of imminent, often fatal, short- and long-term complications (familiar aspiration, pneumonia, oesophageal perforation and oesophageal cancer).

The treatment of Zenker's diverticula is surgical, with the traditional operative solution consisting of transcervical pharyngooesophageal myotomy and resection of the diverticulum. The so-called transoral procedure has been known for several decades, the essence of which is to cut the common wall of the diverticulum and oesophagus together with the upper oesophageal sphincter (using a rigid or flexible) endoscope with a tissue-separating device, resulting in a common lumen (oesophageal diverticulostomy). First described by Mosher (16) in 1917, the ostomy was created using a scalpel and later an electric knife (17) and a carbon dioxide (CO_2) laser, causing much fewer complications. The Endostapler method has also long been known in the management of the Zenker's diverticulum, and minimally invasive access to the diverticulum was reported by Martin-Hirsch and Collard in 1993 (18). The main point of the surgery is to insert a distending operating laryngoscope into the hypopharynx, the longer end of which is inserted into the oesophagus and the smaller end into the diverticulum. The septum between the diverticulum and the oesophagus is then cut with a laparoscopic stapler, connecting the lumen of the diverticulum and oesophagus while interrupting the upper oesophageal sphincter. The endoscopic option has spread rapidly around the world, and several working groups have already reported positive experiences with the use of the method. Our group reported the application of this approach for the first time in Hungary, which is recommended primarily for the elimination of Zenker's diverticulum greater than 3 cm in elderly patients (19). The main advantages of the procedure are shorter surgical time, rare occurrence of complications and absence of surgical scar. Postoperative feeding can be started early, so patients quickly become completely asymptomatic. From an economic point of view, it cannot be neglected that hospital care will also be significantly shortened.

Surgical treatment for an epiphrenic diverticulum is indicated only in the case of complaints, which consists of resection of the diverticulum and, usually, cardiomyotomy. The latter should be complemented with antireflux surgery (Dor or Toupet) to reduce postoperative GERD, which occurs in a large number of cases. Standard explorations of the oesophagus (thoracotomy and laparotomy) are accompanied by significant morbidity. Minimally invasive surgery has become widely used in the functional treatment of the oesophagus and in the surgical treatment of an epiphrenic diverticulum to reduce morbidity. Currently, transhiatal diverticulectomy with cardiomyotomy and antireflux surgery are the most commonly used surgical techniques. In addition to the low morbidity of the method, patients become asymptomatic, and the

intervention provides effective symptom control in 80 to 90% of cases, although publications are limited with regard to long-term results.

The treatment for achalasia is palliative only, and all therapeutic efforts are aimed at facilitating adequate passage through the cardia and, at the same time, preventing late structural and functional oesophageal complications. Besides a few non-operative therapeutic options (endoscopic balloon dilatation [EBD] and botulinum toxin injection [BTI), the safest and most effective treatment for achalasia is still surgery, which involves cutting the muscle fibres of the abnormally functioning LES (a Heller cardiomyotomy). The minimally invasive (laparoscopic and thoracoscopic) types of Heller myotomy were introduced into clinical practice in the early 1990s (21-22). To reduce the risk of GERD following a cardiomyotomy, which had previously been used alone, the procedure was later completed with partial fundoplication (anterior, or Dor, and posterior, or Toupet). This modified laparoscopic Heller cardiomyotomy completed with semifundoplication has proved to be the most effective procedure, with minimal morbidity, both in the short and long term.

In the past, patients with oesophageal diverticula and/or achalasia underwent surgery many times in the absence of advanced diagnostics, in which case they often opted for open surgery with significant morbidity resulting in dubious success. The effectiveness of the surgery at that time in the follow-up period was difficult to assess, and usually the patients' quality of life after surgery was not analysed properly. We wanted to evaluate the success of our surgical interventions and changes in quality of life in patients with the patient-reported outcome (PRO) measurements used more commonly in clinical and pharmacological studies and healthcare analyses. PRO measurements include the HRQL (health-related quality of life) tests that analyse health condition-dependent dimensions of quality of life in individuals. The condition of our patient group was determined with an evaluation scheme similar to a scoring system based on a subjective evaluation of patients known as the "patient symptom score" with data gathered via questionnaires. Due to the nature and relative rarity of the oesophageal motility disorders listed, a limited number of studies have been published even in the universal literature. Most often, small case numbers and summaries were obtained without long-term outcomes from which no meaningful conclusion could be drawn. However, the excellent results of specialized centres and multicentre investigations have convinced critical voices over the years, as a result of which a revolution in minimally invasive technology has also taken place in functional oesophageal surgery. Our institute also has a long tradition of oesophageal surgery, the practitioners of which, in addition to the local application of international guidelines, have

borne continuous innovation in mind. In Hungary, our working group introduced minimally invasive procedures in oesophageal surgery in the 1990s, which has become a standardly used therapeutic alternative in the wake of encouraging results. The care of previously sporadically appearing functional oesophageal diseases has become more specific at the regional level as a result of complex gastroenterological examination and thorough condition assessment, which has been established by a harmonious surgeon–gastroenterologist collaboration. For all these reasons, in the surgical manifestations of pharingooesophageal (Zenker's) diverticulum, epiphrenic diverticulum and achalasia cardiae, we sought to evaluate the factors influencing late quality of life beyond the modern surgical procedure that reflects the current state of science.

2. OBJECTIVES

(1) To compare the perioperative results and the long-term advantages and disadvantages of the two different surgical methods (transcervical diverticulectomy with cricomyotomy [TCD] and transoral stapler diverticulostomy [TSD]) in patients with Zenker's diverticulum (Study I).

(2) To analyse our experience of patients who had undergone laparoscopic-transhiatal diverticulectomy for epiphrenic oesophageal diverticulum focusing on quality of life changes (Study II).

(3) To investigate complex surgical therapy for achalasia concentrating the short- and long-term follow-up results in patients who had undergone laparoscopic Heller–Dor surgery (Study III).

3. PATIENTS AND METHODS

3.1. Patients

Patients who had undergone surgery for Zenker's diverticulum, epiphrenic diverticulum and achalasia between 1 January 2003 and 31 December 2017 were involved in our investigations at the Department of Surgery, University of Szeged.

Study I: Between 1 January 2006 and 31 December 2016, 29 patients (20 males and nine females aged 34 to 89 years) were treated for symptomatic Zenker's diverticulum. The mean age of the TCD group was 65.4 years (34–86 years) with male dominance (12/1), while

the mean age of the TSD group was 68.2 years (47–89 years) equally in both genders (8/8). The most common complaints among the patients scheduled for surgery included severe dysphagia (TCD group: n=11, 85%; TSD group: n=13, 81%) and severe regurgitation (TCD group: n=10, 77%; TSD group: n=11, 69%). Less frequently, patients reported solid food becoming stuck, coughing and reflux. Significant weight loss was observed in the TSD group (25%, 4/16). Patients underwent complex gastroenterological examinations (swallowing X-ray, endoscopy, pH and manometry) before surgery. The preoperative work-up showed an average diameter of 47.7 mm (30–140 mm) of the diverticula, which was almost the same in both groups (TCD: 49 mm [30–120 mm], TSD: 46.6 mm [30–140 mm]). The average duration of symptoms was 31.7 months (3–240 months), subdivided into groups: TCD group 46 months (3–240 months), TSD group 18.6 months (3–72 months). In four patients in both groups (TCD: 30%; TSD: 25%), medically treated GERD was diagnosed in addition to diverticulum. One patient had pneumonia in his past history in the TSD group (6.2%).

Study II: Between 1 January 2003 and 1 March 2016, eight patients (four men and four women; average age: 63 years [52–76 years]) were treated at our department for symptomatic epiphrenic diverticulum. The most common complaint was dysphagia, which occurred in 87.5% (7/8) of the patients. Epigastric pain was experienced by 75% (6/8), and 50% (4/8) reported regurgitation. Moderate weight loss occurred in 62.5% (5/8) of the patients (Table 1). One patient had oesophageal candidiasis in her medical history. The average duration of complaints was 73 months (4–360 months). After we obtained a thorough medical history from the patients, complex gastroenterological check-ups were performed (swallowing X-ray, endoscopy of the upper gastrointestinal tract, pH and manometry of the oesophagus). The average diameter of the diverticulum was 6.5 cm (3–12 cm) before surgery. During the endoscopic examination, diverticula were found an average 34.3 cm (32–38 cm) from the teeth and 5 cm (3–8 cm) from the cardia. They opened mainly in the right, dorsolateral direction (right/left: 5/3). In addition to the diverticulum diagnosis, a small axial-type hiatal hernia was diagnosed in two cases. Manometry of the oesophagus was performed in all cases. Normal LES with prolonged relaxation was detected in two patients (25%), and manometry confirmed achalasia in two cases (25%). The other three findings showed the following: LES with incomplete relaxation and spastic motor disorder (12.5%), incompetent LES (12.5%) and distal oesophageal spasm with involvement of LES (12.5%). One patient had normal manometric findings. pH-metry confirmed abnormal postprandial acid reflux in one case (12.5%), and 50% of the patients had physiological findings (Table 2).

Table 1. Demographics and preoperative data		
Demographics	Gender (F/M)	4/4
	Age (year)	63 (52–76)
Diverticulum characteristics	Diameter (cm)	6.5 (3–12)
	Distance from teeth (cm)	34.3 (32–38)
	Distance from cardia (cm)	5 (3–8)
	Open site (dorsolat. right/left)	5/3

Table 2. Motility findings	
Patients	Oesophageal manometry finding
1	Normal oesophageal and LES function
2	Achalasia
3	Normal pressure, prolonged LES relaxation
4	Normal pressure, prolonged LES relaxation
5	Incompetent LES
6	Incomplete LES relaxation, spastic motility disorder
7	Distal oesophageal spasm with LES involvement
8	Achalasia

Study III: Between 1 January 2008 and 31 December 2017, 54 patients (24 males and 30 females aged 17 to 79 years) with symptomatic oesophageal achalasia were treated at our clinic. The most common complaints among the patients scheduled for surgery included dysphagia, solid food becoming stuck, epigastric pain and, less frequently, weight loss. The

mean duration of the symptoms was 57.3 months (3–192). After a detailed history was taken, patients underwent a comprehensive gastroenterological assessment (a swallowing X-ray exam, upper GI endoscopy, and oesophageal pH-metry and manometry). Based on the Chicago classification, the types of achalasia in the laparoscopic group were as follows: TI, TII and TIII achalasia was found in 30, three and nine cases, respectively; diffuse oesophageal spasm (DES) was confirmed in five cases; and jackhammer oesophagus was observed in one patient. Clinical presentation of megaoesophagus was diagnosed in four cases. 18.7% (9/48) of the patients in the laparoscopic group and all the patients in the acute and the reconstruction groups (4/4, 100%; 2/2, 100%) were treated with preoperative endoscopic balloon dilation.

3.2. Surgery

In our first study, we analysed patients who had undergone two different surgical techniques for Zenker's diverticulum. In 13 cases, transcervical diverticulectomy was performed with cricomyotomy (TCD), andtransoral stapler diverticulostomy (TSD) was carried out in 16 cases. Four patients underwent TCD operation after TSD. The diverticula removed during open surgery were sent for histological examination in every case. Oral intake was gradually built up after a negative leak test. Third-generation cephalosporin was used for antibiotic prophylaxis.

3.2.1. Transcervical diverticulectomy and cricomyotomy

Under intratracheal anaesthesia in the supine position, the patient's head was fixed with the right side and back facing backwards. Exploration and resection of the diverticulum and cricopharyngeal myotomy were performed from an oblique incision made along the medial edge of the sternocleidomastoid muscle. During the open method, diverticula were resected using a straight suturing machine (TX60 Linear Stapler, Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) so that no oesophageal stenosis remained after suturing. The myotomy was then performed from the lower edge of the diverticulum to the oesophagus, approximately 3–4 cm long (Figures 1–3).

Fig. 1. Mobilized Zenker's diverticulum

Fig. 2. Diverticulum resection with stapler

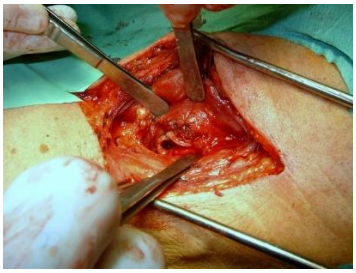

Fig. 3. Cricopharyngeal myotomy

3.2.2. Transoral stapler diverticulostomy

During surgery under intratracheal anaesthesia, the head of the supine patient was fixed in a backward, hyperextended position. The hypopharynx was examined using a rigid, distending operating laryngoscope (Weerda, Karl Storz, Tuttlingen, Germany). Direct visual control was provided with a 5 mm endoscopic camera. The orifices of the oesophagus and diverticulum were explored. The Endostapler (Endo-GIA™ USSC, Norwalk, CT, USA, blue cartridge [45 and 60 mm, respectively]) is inserted into the hypopharynx so that the common wall of the oesophagus and diverticulum is between the stems of the stapler device. By firing the stapler, a V-shaped ostium was formed between the oesophagus and the diverticulum, and its edges were closed with a triple suture row (Figures 4–6).

Fig. 4. Positioning of the laryngoscope

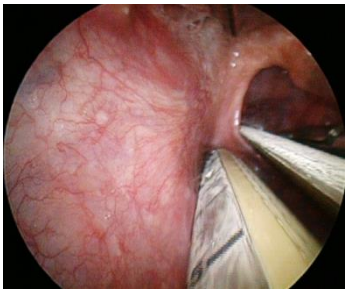

Fig. 5. Stapler diverticulostomy

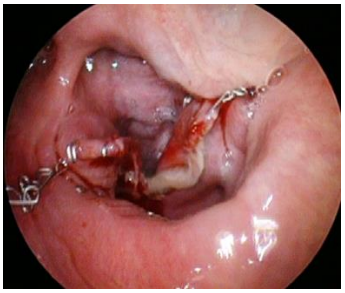

Fig. 6. Intact staple line

After the surgeries, swallowing X-rays were performed with a water-soluble contrast agent (Gastrografin® [diatrizoate meglumine]).

Eighty-seven per cent (24/29) of patients registered for surgical follow-up one month after surgery. During the follow-up examinations, we analysed the change in the complaints compared to the preoperative ones, as well as the radiomorphological difference, if necessary. If patients have complaints later, an extraordinary examination and, if necessary, treatment were performed. In our long-term study (mean 86.1 months, 45–128 months), we wanted to assess the effectiveness of the procedure in terms of symptoms.

Laparoscopic transhiatal epiphrenic diverticulectomy, Heller cardiomyotomy and Dor anterior partial fundoplication were performed on seven patients. One patient only underwent diverticulectomy, where no motility disorder was present. All the surgeries involved an endoscopic check as well. All removed diverticula were sent for histologic examination. Oral nutrition was gradually introduced after a negative swallowing test.

3.2.3. Laparoscopic transhiatal epiphrenic diverticulum resection

Patients were placed in a 30° reverse Trendelenburg position while under general anaesthesia. The surgeon stood between the patients' legs. Three ports were inserted in the abdominal cavity along the left costal arch 15 cm from each other, with one port placed in the epigastrium on the right side and another 10 to 12 mm in diameter, inserted directly above the umbilicus (camera port) (Figure 1). Intraoperative endoscopy was used to assess the level of and clear the contents of the diverticulum. The abdominal and lower mediastinal segments of the oesophagus were mobilized with a LigaSure device (Valleylab, Boulder, CO, USA) (Figure 2). Then the diverticula were dissected and removed with Endo GIA (USSC, Norwalk, CT, USA) blue cartridge (45 and 60 mm) (Figure 3). In two cases, complete removal required two cartridges (one 60 mm and one 45 mm), and in one case, three cartridges (45 mm) were needed. The integrity of the mucosal membrane of the oesophagus was checked with intraoperative endoscopy during all surgeries. The specimen was removed with an Endobag (Medtronic Minimally Invasive Therapies, Minneapolis, MN, USA) (Figure 4). After the diverticulectomy, a Heller oesophagocardiomyotomy was performed on the opposite side of the proximal edge of the neck of the diverticulum in a segment 2 cm in length along the fundus, and then a Dor partial anterior fundoplication was performed (Figures 7–9).

The patients participated in a gastroenterological check-up an average of three months after surgery (swallowing examination, oesophagus manometry, pH-metry and oesophagogastroscopy). Follow-up examinations were performed on six patients, whereas two patients were not present at the scheduled follow-up visits after the initial phase of the follow-

up period (two and six months after the intervention) – although both patients were asymptomatic. Changes in quality of life with regard to symptoms related to oesophageal function were evaluated in our long-term studies (mean, 60 months; 10–138 months) (six patients). A special questionnaire was prepared based on a scoring system published by Eckardt et al. (23) and modified by Zaninotto et al. (24). The score was determined before and after surgery. We asked questions about the severity of regurgitation, dysphagia and epigastric/chest pain since the symptoms had started. All the questions had four possible answers on the frequency of complaints associated with the oesophagus (never, occasionally, daily and at each meal). Answers were weighted. Patients who reported no symptoms received 0 points, and 1, 2 or 3 points were assigned in accordance with the frequency of complaints. The total number of points was 9. After the surgery, we were interested in changes in complaints. Three additional questions were asked on the function of the vagal nerve (feeling full early and frequency of dumping episodes), the regular use of antacids, and change in weight.

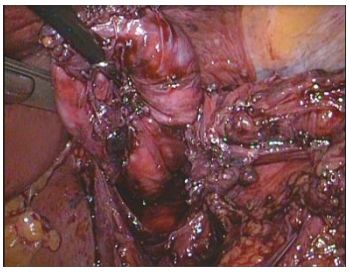

Fig. 7. Fully mobilized diverticulum

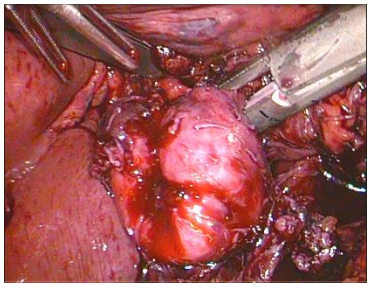

Fig. 8. Diverticulectomy using Endo GIA

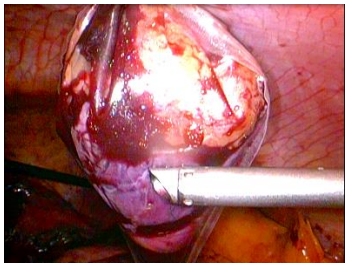

Fig. 9. Specimen removal in an Endobag

In our third study, we measured the effects of different surgical procedures adapted to the diverse clinical appearance of achalasia cardiae.

3.2.4. Laparoscopic Heller–Dor operation

Fourty-eight patients underwent a laparoscopic Heller cardiomyotomy and Dor's anterior partial fundoplication. With the supine patient in a reverse Trendelenburg position, ports were inserted into the abdominal cavity: three ports, with 15 cm intervals, along the left costal margin; one port in the epigastric region, to the right of the midline; and one port (camera port) of 10 to 12 mm in diameter directly above the umbilicus. After creating a pneumoperitoneum, the abdominal, lower mediastinal segment of the oesophagus was mobilized, maintaining an intraabdominal pressure of 15 mmHg. Oesophageal mucosa integrity was checked with intraoperative endoscopy in each case. A Heller oesophago-cardiomyotomy was performed

over a length of 8 cm on the anterior wall of the oesophagus, and over at least 2 cm on the gastric fundus, completed with Dor's partial anterior fundoplication (Figures 10–12).

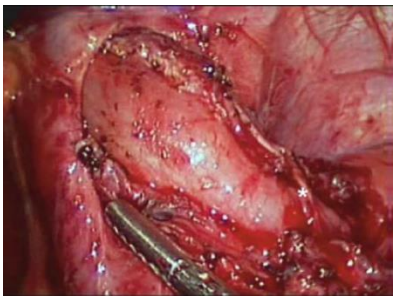

Fig. 10. Lap. Heller myotomy

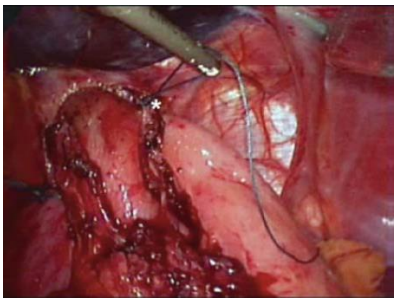

Fig. 11. Lap. Dor fundoplication I

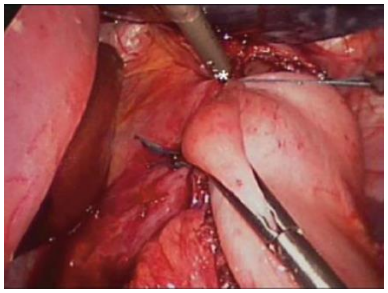

Fig. 12. Lap. Dor fundoplication II

3.2.5. Elective oesophageal resection

Megaoesophagus patients underwent surgery after bowel preparation, as well as ulcer, thrombosis and antibiotic prophylaxis. Gastric replacement involved an upper midline laparotomy, widening the oesophageal hiatus and then mobilizing the oesophagus through the hiatus. After mobilizing the stomach and ligating the left gastric artery, a gastric conduit was created as per Akiyama using linear staplers along the lesser curvature, and then a jejunal feeding catheter was implanted. After drainage, the abdominal section was closed, the patient was turned to a left lateral decubitus position, and the oesophagus was subtotally resected through a right anterolateral thoracotomy with selective intubation. The gastric conduit was pulled from the abdominal cavity through the enlarged hiatus into the thorax, where an anastomosis was performed with a circular stapler between the oesophagus and the stomach.

In a patient who had previously undergone a Heller–Toupet operation and then developed recurrent symptoms and megaoesophagus, the previous fundoplication was eliminated, the lower third of the oesophagus and the cardia were resected, and they were replaced with an isoperistaltic jejunal segment positioned under the azygos vein (the Merendino procedure).

3.2.6. Emergency surgical interventions

Four patients underwent emergency surgery for an iatrogenic oesophageal perforation due to EBD. In two cases, primary suture repair and Heller–Dor surgery were performed with traditional open surgery, using intraoperative endoscopic control, in non-septic patients with

early-stage achalasia (within eight hours). In another two emergency cases, iatrogenic perforation of megaoesophagus was confirmed. More than 24 hours had passed between the injury and the surgical treatment, and the patients were in a severe septic condition at the time of surgery. In one of the patients, the perforation was caused by diagnostic oesophagoscopy performed at another institution, while the other patient developed a rupture after EBD, which was followed by two unsuccessful attempts at endoscopic clipping. Both patients underwent an oesophagectomy as per Torek, a gastrotube was used for decompression purposes, and a jejunal feeding catheter was implanted.

3.2.7. Reconstructive surgery

Ninety-nine and 122 days after Torek's oesophageal resection, successful substernal reconstruction was performed using the right colon and the stomach, respectively.

Postoperative care

For the postoperative period, patients in the laparoscopic group were transferred to the surgery unit after recovery from anaesthesia. Parenteral fluid therapy was administered during the postoperative period. Enteral feeding was gradually introduced after the swallowing X-ray examination was conducted on postoperative day 2 if nothing abnormal was detected. Patients in the elective oesophageal resection group spent three days on average (two to four days) at our department's intensive care unit for close monitoring. Once they were stable, they were transferred to our ward, where they received total parenteral feeding. A swallowing X-ray examination with a water-soluble contrast agent routinely followed on postoperative day 7. If the leak test was negative, the protocol for the gradual introduction of enteral feeding was the same as in the laparoscopic group.

Follow-up

Patients treated with a laparoscopic myotomy were given gastroenterological check-ups (a swallowing X-ray, oesophageal manometry, pH-metry and oesophago-gastroscopy) an average of three months after the surgery – these assessments were carried out in 37 patients. Regular follow-up occurred with a total of 27 patients, while ten patients did not return for the periodic follow-up visits after the initial period (months 2 and 6 post-surgery), although nine of them were complaint-free.

3.3. Conception

In Study I, the results of conventional and transoral surgery were compared in patients with Zenker's diverticulum, analysing the advantages and disadvantages of the different approaches, focusing on the necessity of a redo-operation in the long term (mean 86.1 months).

In Study II, the outcomes of the patients who underwent laparoscopic transhiatal epiphrenic diverticulectomy and Heller–Dor surgery were investigated according to perioperative results and postoperative oesophageal function and its effect on long-term quality of life (average 60 months [10–138 months]).

In Study III, we evaluated the short- and long-term (24 months) results of surgical treatments for variable manifestations of achalasia, including laparoscopic Heller–Dor surgery, with particular reference to changes in postoperative oesophageal function and quality of life.

3.4. Statistics

All data were collected in Excel tables. All statistical analyses were performed with SigmaPlot for Windows (ver. 12.5, 2011 Systat Software, Inc., San Jose, Ca, USA). Values of $P<0.05$ were considered to be statistically significant. The data were collected on an Excel spreadsheet (Microsoft, Redmond, WA, USA). Quantitative data are provided as means (±SD). The paired t test was used to compare pre- and postoperative cumulative mean symptom scores.

3.5. Ethics

The studies were registered with the Regional Human Biomedical Research Ethics Committee with identifiers 4396, 3927 and 4827.

4. RESULTS

4.1. Comparative study of the transoral and transcervical surgical treatment of Zenker's diverticulum: short- and long-term outcomes (Study I)

With minor blood loss (50–100 ml), the mean surgical time was 70 min (TCD group: 98 ± 62 min, TSD group: 42.5 ± 27.5 min, p <0.001). No intraoperative complication occurred in either group. In the TSD group, two patients underwent conventional surgery (15%) due to a cause of visualization problem. One patient in the TSD group (1/16, 6%) underwent reoperation due to bleeding, while another in the TCD group was confirmed as having pneumonia (1/13, 7%) (Table 3).

Table 3. Perioperative clinical data (TSD and TCD patients)

	TSD	TCD
Gender (F/M)	8/8	1/12
Age (years)	68.2 (47–89)	65.4 (34–86)
Mean diverticulum size (mm)	46.6 (30–140)	49 (30–120)
Operative time	42.5 (15–70)	98 (36–160)
Visualization difficulty (n,%)	n=2 (15 %)	
Staple line leak (n)	0	0
Complication requiring reoperation (n)	1 (bleeding)	
Mortality	0	0
Onset of oral feeding (day)	2.9 (1–7)	4.6 (3–7)
Hospital stay	7.3 (5–10)	9.7 (7–12)

Postoperative control swallowing X-ray showed no abnormality in any of the cases. After a negative leak test among the patients, we gradually built up their oral diet and discharged them without complaints on an average of 3.7 days (TCD: 4.6 ± 2.6 days; TSD: 2.9 ± 2 days, p<0.001). The mean hospital stay was 9.7 days (7–12 days) in the TCD group and 7.3 days (5–10 days) in the TSD group (p<0.001) (Table 3). Histological examinations of the diverticula did not show any dysplasia or malignancy. No suture line insufficiency (0/29, 0%) and no perioperative mortality occurred. After one month, 62.5% of the patients were symptom-free

(15/24). After late follow-up, patients' quality of life improved significantly, and their severe preoperative symptoms, mainly dysphagia and regurgitation, were reduced to a minimum or completely eliminated. In the TSD group, we found a recurrent complaint in half of the patients (6/12, 50%), and transcervical surgery was performed later in four (4/12, 33%) cases. The main complaints of patients who received re-intervention were severe regurgitation (2/4), severe dysphagia (1/4) and, in one case, a combination of the two complaints (1/4). Of these, three patients complained half a year after the primary surgery, while four of them reported complaints four years after the primary surgery (Table 4).

Table 4. Reintervention group after TSD

Primary operation	Second operation	Duration between procedures (months)	Onset of recurrenty complaints after primary operation (months)	Complaints
TSD	TCD	96	48	Dysphagia + Regurgitation
TSD	TCD	9	6	Regurgitation
TSD	TCD	10	6	Regurgitation
TSD	TCD	84	6	Dysphagia

In the TSD group, one patient's (6.2%) dysphagia complaints were resolved though regurgitation was occasionally reported, while another developed moderate dysphagia (6.2%). In patients requiring repeated intervention (TCD), one case of cervical abscess developed one month after transcervical surgery. Her condition gradually improved after drainage surgery, and she is currently without complaints, with swallowing function maintained. In the TCD group, one patient developed persistent hoarseness with satisfactory swallowing function (5.8%), while another (5.8%) had severe regurgitation but moderate dysphagia.

4.2. Laparoscopic surgery for epiphrenic oesophageal diverticulum: short- and long-term outcomes (Study II)

The duration of the surgery was an average of 165 (130–195) minutes with minimal blood loss (50–150 mL), and conversion was not necessary. One patient developed bleeding in the early postoperative period (through an abdominal silicon drain 3 h after the primary operation). Despite hemostatic medications, the bleeding did not stop, and thus a second laparoscopy was required. There was active bleeding from the oesophageal myotomy line, which was controlled with a high-energy device (LigaSure). No sign of postoperative bleeding was observed thereafter, and the patient recovered fully after the operations. A swallowing test performed with the administration of a water-soluble contrast agent diatrizoate meglumine) on postoperative day 4 confirmed leakage along the sutures in one case (1/8, 12.5%). Because the conservative treatment (zero diet, antibiotic therapy and parenteral feeding) was not successful for seven days, we decided to implant a jejunal feeding catheter to accelerate the healing process. After another seven days of conservative treatment after the intervention, the fistula closed; thereafter, oral feeding was built up. There was no mortality. After a negative swallowing test, oral nutrition for patients was phased in gradually, and patients were discharged without any complaints. Average duration of care was 14 days (8–41 days) (Table 5). A histology of the diverticula showed no dysplasia or malignancy, but oesophageal manifestation of Crohn's disease was confirmed in one sample. After the surgeries, functional tests were performed on three patients (gastroscopy, manometry and pH-metry), which showed normal function. The other five asymptomatic patients refused all tests except gastroscopy.

Table 5. Perioperative clinical data

Operative time (min)	165 (130–195)
Blood loss (ml)	100 (50–150)
Conversion (n)	0
Intraoperative complications (n)	0
Staple line leak (n)	1
Complications requiring reoperation (n)	1 (bleeding)
Mortality (n)	0
Hospital stay (mean, days)	14.1 (9–41)

Six patients (6/8, 75%) completed the questionnaires on long-term symptoms. The results were compared with preoperative complaints based on thorough medical histories. A pre- and postoperative subjective "individual complaint score" was therefore determined. The oesophagus-related mean cumulative score before the intervention was 6.3 (3–9), and it dropped to 1.6 (0–5) after the intervention, which is an average of 74% ($p<0.001$) subjective improvement (Table 6). Among the patients completing the questionnaire, four (66%) experienced weight gain, and none reported weight loss (0%). A symptom characteristic of dysfunction of the vagal nerve was detected in only one patient (12.5%) and was often associated with occasional early fullness. Proton pump inhibitor (PPI) therapy was started in four patients who had GERD develop after a six-month (2–12 months) complaint-free period in the case of four patients. In three cases, complaints were resolved with drug therapy. In one patient, laparoscopic antireflux surgery (Nissen) was performed because conservative therapy had been ineffective, and the patient became completely asymptomatic by the first six-month follow-up visit.

Table 6. Oesophagus-related symptoms; change of individual complaint scores

Symptoms	Preoperative severity mean score (points)	Postoperative severity mean score (points)	Symptom relief (%)	Statistics
Dysphagia	2.5 (0–3)	0.17 (0–1)	93.3	
Epigastric pain	1.83 (0–3)	0.83 (0–3)	55.5	
Regurgitation	2 (0–3)	0.66 (0–2)	66.6	
Mean (SD) cumulative score/patient	6.33 (±2.06)	1.66 (±1.86)	74	$p<0.001$

4.3. Complex surgical treatment of oesophageal achalasia in the era of minimally invasive surgery (Study III)

The average duration of the laparoscopic procedures was 72 minutes (62–90 minutes) with minimal blood loss (50 to 100 mL). No intraoperative complications were observed, and conversion was required in one case (1/48, 2%) for adhesions. The swallowing test conducted with a water-soluble contrast agent (Gastrografin®) on postoperative day 4 (on average) revealed a leak from the site of the sutures in one case (1/48, 2%), which was treated with emergency reoperation and suture placement. The average length of stay was 7.3 days (5–28 days) in the elective, laparoscopic group.

There was one case of hydrothorax formation requiring a puncture and one case of atrial fibrillation in the emergency surgery group. There were no mortalities. Patients with primary suture repair were discharged after 16.5 days (13–20 days), following a swallowing X-ray with normal results, while those who had undergone Torek's operation were discharged after 15.5 days (14–17 days). Later, reconstructive surgeries performed with a colon or gastric pull-up after Torek's operation were accompanied by neither intraoperative nor postoperative complications, and patients were discharged on day 14.5 after a swallowing X-ray with normal results and gradually introduced oral feeding (Table 7).

Table 7. Perioperative data and outcomes of different achalasia surgeries

Indication for surgery	Surgery	Age (mean, years)	Type of surgery	Timing of surgery	Morbidity (%)	Mortality (%)	Hospital stay (mean, day)
	(N)						
Achalasia (early stage)	48	46.2	Laparoscopic Heller–Dor	Elective	2% (1/48)	0	7.3
Achalasia (advanced stage, mega-oesophagus)	2	43.3	Oesophageal resection with gastric, jejunal or colonic replacement	Elective	0.00%	0	18.6
Achalasia, iatrogenic injury, early diagnosis (<24 hours)	2	65.5	Primary suture	Emergency	50% (1/2)	0	16.5
Achalasia, iatrogenic injury, late diagnosis (>24 hours)	2	60.5	Total oesophagectomy (Torek's operation	Emergency	50% (1/2)	0	15.5
Late reconstruction after Torek's operation	2	60.5	Reconstructive surgery with gastric or colonic replacement	Elective	0.00%	0	14.5

Long-term follow-up

At the 1–6-month follow-up visit, all the patients, except for one, reported unrestricted swallowing, which was also confirmed by the functional assessments. Those returning for later gastroenterological check-ups were evaluated based on follow-up intervals and their swallowing function (Table 8).

Table 8. Follow-up data after laparoscopic Heller–Dor procedure

Follow-up interval	First follow-up	6–12 months	12–24 months	>24 months
Proportion of patients with complaint	1/48 (2%)	8/48 (16.6%)	10/48 (20.8%)	9/48 (18.7%)
TI	1/30 (3.3%)	5/30 (16.6%)	4/30 (13.3%)	4/30 (13.3%)
TII	0/3 (0%)	0/3 (0%)	0/3 (0%)	0/3 (0%)
TIII	0/9 (0%)	3/9 (33.3%)	3/9 (33.3%)	2/9 (22%)
DES	0/5 (0%)	0/5 (0%)	3/5 (60%)	3/5 (60%)
Jackhammer	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Postoperative reflux	0/48 (0%)	0/48 (0%)	3/48 (6.2%)	3/48 (6.2%)
Postoperative dysphagia	1/48 (2%)	8/48 (16.6%)	8/48 (16.6%)	7/48 (14.5%)

At the 6–12-month follow-up visit, non-severe recurrent dysphagia was reported in eight patients. In two cases, dietary changes and medical treatment resulted in notable improvement, while persistent complaints were recorded despite therapy in two others. EBD was indicated in an additional four cases (8.3%), with one of these patients requiring oesophageal resection for recurrent complaints despite the EBD, considering the patient's young age and the significantly dilated oesophagus. At the 12–24-month visit, the number of patients being followed up for dysphagia (8) had not changed, but there were three new cases. Medical therapy was successful in one, and a successful EBD was performed in another; however, one patient had persistent complaints. During the follow-up visits after 24 months, a total of seven patients were followed up for dysphagia, one of them being a new patient, who became complaint-free after conservative therapy. Those with complaints despite surgery mostly suffered from spastic motility disorders (TIII and DES).

Postoperative reflux did not occur during the 6–12-month follow-up period, while it developed in three patients in total (3/48, 6.2%) during the 12–24-month and >24-month follow-up; however, it was controlled well medically.

Our study also revealed that at the 12–24-month follow-up visits, symptomatic and symptom-free patients had undergone surgery at approximately the same age (53.5 years vs. 48.1 years), and the duration of symptoms was longer in symptomatic patients (20.3 months vs. 112.8 months). However, there was no difference in preoperative EBD (symptom-free 11% vs. 10%). During the >2-year follow-up, there was still no difference in age (53.1 years vs. 54.8 years), and patients with satisfactory symptom control underwent surgery later than those in the symptomatic group (82.2 months vs. 40.5 months).

5. DISCUSSION

The treatment tactics of oesophageal motility diseases have undergone unbroken development over the years with the patenting of technological advances and the introduction of modern gastroenterological diagnostics that help to establish a correct surgical indication. As a result, standardized care has emerged in specialized centres that not only focuses on direct clinical conditions, but also includes a specific algorithm for assessing the success of treatment and the effects of interventions during patient follow-up. Minimally invasive surgical procedures on the oesophagus, with adequate proficiency and a stable radiological, internal medicine and intensive care infrastructure, no longer carry an extreme risk, and the surgical burden is significantly lower than in conventional surgeries. Together, these factors result in rapid recovery of patients and a good long-term quality of life. However, these benefits can only be realised if all professionals responsible for diagnosing and treating the patient agree on an individualized treatment, in other words, to help find the best option for the situation, be it conservative or surgical. The surgical solution for functional diseases of the oesophagus can actually be considered palliative, as there is no possibility of causal treatment according to the current state of our science. In fact, all operative efforts are aimed at eliminating the already established abnormal muscle function and the resulting secondary pathological manifestations (diverticula and oesophageal dilatation) in order to prevent potential subsequent serious complications (esophageal perforation and oesophageal cancer). For this reason, it is extremely important that patients who seek medical attention for upper gastrointestinal syndrome receive the highest possible standard of treatment, regardless of whether they are young or old. Based on the literature, the benefits of the minimal access approach and less radical surgery of the oesophagus in all cervical, thoracic and abdominal sections are indisputable, their efficacy is outstanding, and the results of late follow-up are convincing.

Nowadays, the benefits of minimally invasive surgical procedures are manifold. The transoral stapler method for Zenker’s diverticulum is an intervention that provides excellent functional results with a significantly shorter surgical time. Laparoscopic-transhiatal diverticulectomy with Heller cardiomyotomy and semifundoplication represent the gold standard procedure in the surgical treatment of epiphrenic diverticulum, which develops as a result of motility disorder. Due to the smaller access, less postoperative pain and faster recovery time are characteristic of the patient group, while hospital nursing time is also significantly reduced. Laparoscopic Heller–Dor surgery for achalasia cardiae is one of the most accepted minimally invasive procedures in the surgical treatment of achalasia cardiae. In addition to low morbidity,

the procedure provides a significant proportion of long-term asymptomatic symptoms; other favourable factors include the opportunity to explore the lower third of the oesophagus well through the hiatus and to perform myotomy and antireflux surgery with technical precision.

Since the introduction of the minimally invasive technique in 1998, its prevalence and popularity have been increasingly observed in our clinic, based on experience gained and positive feedback from patients. In my doctoral dissertation, I want to report on the surgical therapy of three separate, yet functionally unified entities from different approaches and their special manifestations, focusing on the essential perioperative aspects and the patients' long-term quality of life.

5.1. Comparative study of the transoral and transcervical surgical treatment of Zenker's diverticulum: short- and long-term outcomes (Study I)

Both surgical procedures performed by our team (TSD and TCD) are operations with the same low morbidity and satisfactory long-term results as the world literature data. In the present study, no deaths occurred; in one case, we observed more significant postoperative morbidity: one reoperation was needed due to bleeding, and pneumonia developed in another case. TSD surgery lasted significantly shorter, and oral feeding was started earlier; however, recurrent/residual complaints occurred during follow-up, which necessitated four transcervical surgeries. There was no reintervention due to recurrent complaints in the TCD group. However, one patient in the TCD group developed persistent hoarseness, presumably due to a recurrent laryngeal nerve lesion associated with cervical dissection. In the case of surgical treatment of Zenker's diverticulum, four basic issues definitely need to be discussed: the size of the diverticulum, the age of the patient, the issue of cricomyotomy and the choice of the best approach.

The treatment strategy for Zenker's diverticulum under 2 cm is determined by cricomyotomy alone; no resection is required. After a stapler diverticulostomy performed transorally, the residual common septum between the oesophagus and the diverticulum is often seen, a condition that may raise the question: for which diverticulum size is transoral therapy optimal? Ozgursoy et al. recommend transoral surgeries for lesions between 3 and 6 cm (25). Consistent with the literature, our observation also shows that despite the benefits of a progressive minimally invasive era, patients with diverticulum sizes below 2 cm and above 6 cm do not benefit from endoscopic therapy. This can be explained by the fact that septotomy is not sufficient for a small diverticulum, while for larger ones a massive septum must be cut, which

poses potential dangers: elevated bleeding complications with high-energy cutters, higher suture failure rates after stapler use and the pocket may cause regurgitation in the long term (26-27). Regardless of the different approaches to surgeries, one concept has not changed over time: the development of Zenker's diverticulum is based on dysfunction of the cricopharyngeus muscle, so its myotomy is the key (28). Previous studies have clearly attributed the reason for the recurrence of diverticula to a previous insufficient myotomy (29). The open procedure carries a higher risk as regards longer operative time and recovery period. Minimizing the risk of surgical trauma is crucial in patients with Zenker's diverticulum, who are usually in or beyond their seventies and suffering from chronic diseases resulting in a worse general condition. The transoral (rigid or flexible variant) access could thus be an ideal solution for patients with less reserve capacity.

The possible complications may obviously vary according to the approaches. In the transoral group, the most frequent ones are mediastinitis (1.2% vs. <0.3%) and cervical emphysema (3.0% vs. <0.1%), while fistula formation (3.7% vs. 1.2%) and recurrent nerve injury (3.4% vs. <0.3%) occur often in the open group. Disadvantages of endoscopic therapy include technical failure and recurrent complaints. Review studies report a 30% visualization problem, but the largest single-centre endoscopic study by Wilken et al. shared a 3.9% result in 337 patients (30). It is well-known that smaller diverticulum size is associated with less effective endoscopic success, although Wilken's analysis did not confirm this finding, while a recent comparative study reported an endoscopic recurrence of 39% (31). The failure of this approach results in incomplete diverticulostomy and insufficient dissection of the muscle, which may be responsible for persistent/recurrent complaints. It is indisputable that the completeness of myotomy, whether open or endoscopic, is an essential part of a standard surgical solution. The results of Verdonck et al. were an overall failure rate of 18.4% for endoscopy and 4.2% for the open method, which includes short-term failure (inadequate visualization) and early recurrence (32). Examining short-term success separately, the open solution proved to be more advantageous (endoscopic: 9.3% vs. open: 1.3%). With endoscopic exploration difficulties of 5.2%, long-term late recurrence rates of 2.9% for the open method and 3.9% for endoscopy were confirmed in the long term (33). In our study, visualization difficulties occurred in two patients, because of which surgery was continued transcervically (15%).

In our present clinical investigation, we wanted to introduce oral feeding after a negative leak test. Our team ordered a swallowing X-ray with a water-soluble contrast agent on the fourth postoperative day in the TCD group and on the second postoperative day in the TSD group.

Although the TSD method is a quick and technically feasible intervention, it is not always a perfect choice, as the patient's anatomical features (inability to reach the hyperextended neck, degenerative musculoskeletal disorders and visualization difficulties due to insufficient mouth opening) and diverticulum parameters (diverticulum size below 3 cm, short septum between the diverticulum and oesophagus, and diverticulum size above 6 cm) could be sources of failure. To overcome the short septum-associated difficulties, many technical innovations and manoeuvres have spread (e.g. pulling the suture to the septum and septal membrane precut before stapler positioning), which provide alternatives to conversion (34). There are parameters based on anthropometric results, especially in anaesthesia, which have a prognostic value on the success rate of a certain method (mouth opening in mm, BMI, thyromental distance, and Mallampati and Cormack scores).

Along with open and rigid endoscope procedures, it is essential to note the alternative provided by flexible endoscopy. The use of flexible endoscopy has gained popularity to eliminate negative factors (35-36), while the benefits of a minimally invasive technique have not been compromised. Flexible endoscopy preserves the principle of rigid endoscopy, namely, by creating a common lumen by cutting the common septum, automatically performing the myotomy. The intervention is officially consistently referred to as flexible endoscopic septotomy (FESD), and high-risk elderly patients benefit most from it (37). The method is fast and efficient, it can be performed in inpatient and outpatient settings, and it requires no special anaesthesia (38). Some centres offer this option directly to all Zenker's diverticulum patients, but most authors agree that the method is rather reserved for "high-risk" patients in whom the anatomical features of the head and neck do not allow rigid endoscopy to be performed (39). Nowadays, the flexible endoscopic procedure is already available in Hungarian practice. Gyökeres et al. performed 30 interventions (including six reinterventions) over five years with the same complication and recurrence rates as the world literature data (40). Studies comparing flexible endoscopy and Endostapler report similar results in terms of hospital stay, symptom improvement and incidence of complications; however, the duration of intervention is longer in the Endostapler group. In terms of clinical efficacy, flexible endoscopy shows a varied picture with a success rate of 56–100%, in which dsyphagia improvement reached 84–100% [6,7,25]. Using flexible endoscopy, an approximately 20% recurrence is expected based on current literature data (37). Predictors of recurrence may be pre-treatment diverticulum size more than 5 cm, post-treatment diverticulum size more than 1 cm and septotomy length less than 2.5 cm. Antonello et al. successfully demonstrated the efficacy of flexible endoscopy in

both open and rigid endoscopic recurrences after achieving 84% complete complaint relief in the study group (41). Complications of the procedure include cervical abscess/mediastinitis (0–27%) and bleeding (0–10%) due to perforation (39). Prospective, randomized studies comparing different interventions are scant in the literature, and the publications considered are retrospective and contain a number of uncertain parameters. Nonetheless, it can be seen that both endoscopic and open methods are safe and predominantly alleviate complaints. In addition, it is necessary to analyse the particular technique in terms of long-term swallowing function (42). According to the study conducted by the latter working group, better long-term complaint relief was achieved in patients in the open group. The idea that endoscopic therapy is easier to perform than a traditional excision (unless the procedure is performed in an oesophageal centre) is debated, so it is difficult to say that the endoscopic solution is not the first choice; however, in the case of limited visualization and reoperation, the open route is more advantageous. Previous cervical surgeries, poor general condition and advanced age all call for less surgical time and trauma, thus suggesting a choice of endoscopic therapy. An open mode is recommended for young patients in good health due to proven better long-term outcomes and low probability of corrective surgery (43). Whatever the mode of intervention, the experience of the surgeon and the preference of the patient are decisive in choosing the optimal procedure. In the present study, swallowing function improved in patients in both groups. Our results investigating the postoperative swallowing function confirm that a large percentage of complaints remain after transoral procedures, which need to be corrected with another, preferably open surgery. In our own study, we demonstrated that the main complaints of our patients were severe and regular dysphagia and regurgitation, which almost completely disappeared after TCD surgery. In the TSD group, due to permanent complaints, four (4/29, 13.7%) cases needed to undergo further surgery. Then the transcervical diverticulum resection and cricomyotomy resulted in complete asymptomatic relief.

5.2. Laparoscopic surgery for epiphrenic oesophageal diverticulum: short- and long-term outcomes (Study II)

Laparoscopic transhiatal epiphrenic diverticulum resection with the Heller–Dor surgical method, which we use, is an intervention with low morbidity and adequate long-term results comparable with international data. Partial insufficiency of mechanical suture was detected in one case (1/8; 12.5%), which was resolved with conservative therapy, and no perioperative mortality occurred. Patient follow-up lasted for an average of 60 months, quality of life

improved significantly, and symptoms detected before surgery decreased to a minimum. Although half of the patients exhibited GERD symptoms, the reflux was controlled with drug therapy in three cases. Another surgical intervention (Nissen surgery) was necessary because of persistent symptoms in one case.

Morbidity from the intervention is minimal, and it provides symptom relief in 85 to 100% of cases. With a prevalence of 8 to 23%, staple line insufficiency is one of the most frequent and serious complications after an oesophageal diverticulum resection. Mortality is low (0%–7%) (11,44). In addition to the well-known advantages of laparoscopy (e.g. less postoperative pain and shorter hospitalization), other favourable factors with this procedure include the ability of the surgeon to explore the diverticulum thoroughly from the transhiatal direction, remove it easily with an Endostapler (Medtronic Minimally Invasive Therapies), and then perform myotomy and antireflux surgery in a technically adequate manner. Intraoperative endoscopy aids in identifying the diverticulum, in aspirating its contents and in dissecting it correctly as well. The safety of the surgery is significantly increased by an endoscopic check at the time of the resection and a check of the sutures after diverticulectomy (45).

There are two important questions as regards minimally invasive surgery for epiphrenic diverticulum that should be discussed: the necessity of cardiomyotomy and antireflux surgery. The choice of surgical method is determined not only by the size of the diverticulum, but also by the associated motility disorder; therefore, removal of the diverticulum alone is not sufficient to prevent complications and to provide an asymptomatic condition. Data in the literature confirm that suture insufficiency and the incidence of disease recurrence are more common after surgery performed without myotomy (46). A study conducted with 21 patients at the Mayo Clinic showed high rates of suture insufficiency and disease recurrence (24 and 19%, respectively) in patients without myotomy after diverticulectomy, whereas these sequelae did not occur in the myotomy group (47). The required length of the myotomy is still debatable. Long myotomy is well-known (10), although several publications and our own data confirm the necessity of an intervention of 1.5 to 2.0 cm in length from the upper edge of the diverticulum to the proximal segment of the stomach (4,48–50). Other data suggest that the length of the myotomy should be the same as the extent of motor dysfunction (51). In accordance with a North American study, in the case of achalasia and an epiphrenic oesophageal diverticulum, myotomy without resection and partial fundoplication resulted in clear improvement in quality of life (52). If a myotomy is necessary, surgery must be complemented with an antireflux procedure as well. Most surgeons prefer partial fundoplication

(Dor or Toupet), as this procedure avoids hypertension in the LES and decreases the incidence of GERD (50). However, others recommend complete fundoplication, as their results show that this procedure does not increase postoperative dysphagia and provides better reflux control (4,53). Not all articles with long-term data mention postoperative reflux. We found four publications that covered GERD (4,51,53,54) with precise documentation and complete functional tests. Reflux disease occurred in only a few cases, irrespective of the type of fundoplication (Dor, Toupet or Nissen). Rosati et al. reported on a patient who was prescribed a PPI for the symptoms (1/20) (54).

In our complicated case, preoperative investigations revealed no motility disorder; therefore, a laparoscopic transhiatal diverticulectomy was performed, but no cardiomyotomy. We carried out a complete resection of the diverticulum with three cartridges of 45 mm Endo GIA (Medtronic Minimally Invasive Therapies). Our theory is that both the absence of cardiomyotomy and the step formation on the oesophageal staple line caused by the multiple cartridges contributed to the staple line insufficiency. According to these results, cardiomyotomy should be considered to minimize staple line insufficiency in all cases.

We wanted to evaluate the success of our surgical interventions and changes in quality of life in patients with the patient-reported outcome (PRO) measurements used more commonly in clinical and pharmacological studies and healthcare analyses. PRO measurements include the HRQL (health-related quality of life) tests that analyse health condition-dependent dimensions of quality of life in individuals. The condition of our patient group was determined with an evaluation scheme similar to a scoring system based on a subjective evaluation of patients known as the “patient symptom score” with data gathered via questionnaires. This score was used by an Italian group for evaluating the outcome of epiphrenic diverticulum (55). Questionnaire-based analyses have been used for several benign oesophageal diseases. A publication by a Cleveland group should be noted (29) that compared quality of life after open surgery and endoscopic treatment of Zenker’s diverticulum based on telephone interviews (42). Patients with achalasia with an oesophageal diverticulum who underwent surgery reported their complaints and satisfaction at regular intervals on a scale of 1 to 10 (56). In the latter cases, 76% of patients undergoing laparoscopic Heller–Dor surgery and diverticulectomy were satisfied: 31% of them considered improvement in symptoms to be excellent, and 27% considered it to be good. In a long-term study, Rosati et al. confirmed a permanent asymptomatic condition in 85% of patients undergoing laparoscopic treatment of epiphrenic

oesophageal diverticula (54). Zaninotto et al. considered improvement of more than 50% in the patient symptom score to be successful, and this was the case in 70.8% of the patients (55).

5.3. Complex surgical treatment of oesophageal achalasia in the era of minimally invasive surgery (Study III)

The treatment strategy for patients with achalasia in centres specialized in oesophageal diseases is determined by close cooperation between gastroenterologists and surgeons. In addition to the ever growing variety of effective medical interventions, patients with persistent symptoms may undergo surgery at different stages and with different timings. The first documented surgery for achalasia was performed by Ernst Heller in 1913; it was an extramucosal myotomy at the level of the cardia, thus reducing the pressure of the LES and facilitating the passage of solid food into the stomach (57). Originally, Heller recommended a double (anterior and posterior) myotomy; however, a simple myotomy, a procedure still used today, was described by Zaaijer, a Dutch surgeon, in 1923 (58). The traditional open surgeries of the oesophagus (via thoracotomy or laparotomy) have considerable morbidity rates. To reduce them, the minimally invasive surgical technique is currently an excellent alternative in the surgical treatment of functional disorders of the oesophagus, including oesophageal achalasia. Our team has published several papers on its favourable results in the minimally invasive surgical treatment of benign oesophageal disorders (59-64). In addition to the well-known benefits of laparoscopy (less postoperative pain, shorter hospital stay and better cosmetic results), a further favourable factor is that the lower third and the abdominal segment of the oesophagus can be well explored through the hiatus and that, technically, a myotomy and antireflux surgery can be performed with precision.

Beyond an accurate diagnosis, medical treatment for achalasia is determined by the physical capacity of the patient and their response to therapies. Smooth muscle relaxants and botulinum toxin injected into the lower oesophageal sphincter may reduce dysphagia; however, their effect is only temporary, and they may make a later Heller myotomy more difficult (65-67). The efficacy of EBD is between 70 and 80% (68), and newer comprehensive studies have confirmed a perforation rate of less than 1%, which equals the rate of perforations not noticed during Heller surgery (69). Although the rate of a favourable clinical response to a surgical myotomy is better than that after EBD, serial EBD may be an appropriate alternative to surgical treatment (70). In a prospective, randomized study conducted by Moonen et al., nearly the same success in

dysphagia control was demonstrated after five years; however, this was only achieved after multiple dilations in one-quarter of the EBD group (71). Persson et al. demonstrated a significantly higher five-year symptom-free rate after LHM than after EBD (95% and 65%, respectively) (72), and the same trend was confirmed by three different meta-analyses (73-75). When assessing the effect of different clinical parameters on therapy, it was also shown that patients below the age of 45 years benefited more from the surgical treatment than from EBD (76).

POEM, which requires a serious learning process and a special surgical environment, is also not a clear alternative to minimally invasive surgical treatment (77-78). One of the main concerns with POEM is the high rate of gastroesophageal reflux, which develops after treatment. It appears, however, that this method is useful with type III achalasia, where it can ensure a longer myotomy than standard LHM; at the same time, the efficacy of LHM is almost 85% here as well (79). Another possible future indication for this procedure is recurrent and unsuccessful cases (80).

Laparoscopic Heller–Dor surgery

Laparoscopic Heller–Dor surgery was introduced at the end of the last century and since then has become the gold standard in the surgical treatment of oesophageal achalasia. It has excellent mortality and morbidity rates of 0.01% and 6%, respectively, (73,81; Table 9) and it provides a long-term symptom control rate of about 90%, the success of which also depends on the Chicago classification (79). Mucosal injury may occur during the procedure in 6.9% (0–33%) of cases, and it may remain hidden in most cases or may be treated immediately during surgery (73).

Table 9. Landmark clinical studies investigating laparoscopic Heller–Dor operation

Author	Year	Study design	Procedure type	Sample size (N)	Follow-up (month)	Complication rate (%)	LOS (day)	Success rate (%)	Postoperative GERD (%)	Postoperative dysphagia (%)
Ancona[33]	1995	RC	LHMD	17	6	0%	4	94.2%	0%	5.8%
			OHMD	17	6	0%	10	94.2%	5.8%	0.0%
Richards[39]	2004	RCT	LHMD	22	6	0%	1	NA	by pH: 9.1 %	0.0%
			LHM	21	6	0%	1	NA	by pH: 47.6 %	
Boeckxstaens[23]	2011	RCT	LHMD	106	24	12%	NA	90%	by pH: 23%, by EGD: 21%	6.6 %
			EBD	95	24	4%	NA	86%	by pH: 15%, by EGD: 19%	
Moonen[24]	2016	RCT	LHMD	105	60	11%	NA	84%	by pH: 34%, by EGD: 18 %	NA
			EBD	96	60	5%	NA	82%	by pH: 12%, by EGD: 14 %	
Costantini[29]	2019	CCS	LHMD	140	24	2.1%	3	95.7%	by pH: 17.1%, by EGD: 15.2%	NA
			POEM	140	24	5%	2	99.3%	by pH: 38.4%, by EGD: 37.4%	
Werner[30]	2019	RCT	LHMD	109	24	7.3%	NA	81.7%	by pH: 30%, by EGD: 29%	NA
			POEM	112	24	2.7%	NA	83%	by pH: 30%, by EGD: 44%	
Costantini[45]	2018	RCT	LHMD	1001	62	4.7%	3	89.5%	by pH: 9.1%, by EGD: 11.6%	NA
Rawlings[42]	2012	RCT	LHMD	36	12	5.6%	NA	90.9%	by pH: 41.7%	8.3%
			LHMT	24	12	8.3%	NA	93.1%	by pH: 21.1%	4.1%
Torres-Villalobos[41]	2018	RCT	LHMD	38	24	2.6%	2.5	100%	by pH: 10.5%	NA
			LHMT	35	24	0%	2.5	90%	by pH: 31.5%	NA
Kumagai[40]	2014	RCT	LHMD	19	12	0%	2	90.9%	by pH: 18%	18.0%
			LHMT	22	12	4.5%	2	85.7%	by pH: 38%	14.0%
Rebecchi[44]	2008	RCT	LHMD	72	60	2%	3.2	97%	symptoms: 5.6%, by pH: 2.8%	2.8 %
			LHMN	72	60	1%	3.6	85%	symptoms: 0%, by pH: 0%	15.0%

Based on our own results, it can be established that the success rate beyond 24 months is 85.5%, which can be considered 93.7% with the supplementary conservative medical treatment of symptomatic patients. In the patient group studied, one patient in total (1/48, 2%) developed a surgery-related complication, oesophageal mucosal lesion, which was discovered with the swallowing X-ray performed with a water-soluble contrast agent on postoperative day 1. The injury was supposedly caused by intraoperative thermal damage, which was not seen during the endoscopic follow-up exam after the primary surgery. No complications were observed in the other 47 patients (98%) in the group, and there was no mortality. All in all, the clinical results of this study are clearly consistent with international standards, considering both long-term symptomatic control and the morbidity rate.

As to LHM, there are two issues to be discussed: achieving a symptom-free status post-surgery (eliminating dysphagia) and the course of postoperative reflux. Both factors can basically be traced back to the proper performance of the myotomy. The 2018 ISDE (International Society of Diseases of the Esophagus) guidelines on achalasia state that a laparoscopic Heller myotomy is recommended over a length of at least 6 cm on the oesophagus and 2 to 3 cm on the stomach for effective control of symptoms (82). Two publications reported a myotomy that extended 3 cm onto the stomach, which reduced the risk of delayed dysphagia (83-84). Proximally, a myotomy of 6 to 8 cm in length is recommended in general, but no comparative publications are available on the length of oesophageal myotomies (85). There is also a physiological basis to the proper cutting of the fibres – the high-pressure zone of the cardia is generally slightly shorter than 4 cm and extends 2 cm from the Z-line in the oral direction.

Based on our previous clinical study, it is clear that an inadequate myotomy, either in the aboral or the oral direction, may cause recurrent symptoms, which can be corrected with repeat surgery (86). Our current study also demonstrates that recurrent symptoms are more common in patients with a spastic-type oesophageal disorder (TIII achalasia and DES) than in those with TI or TII disease. Our results are expressive primarily after twelve months, although symptoms returned earlier among TIII cases (3/9, 33%). The trend continues in the 1–2-year follow-up period, since the rate of symptomatic patients is relatively high in the spastic group (TIII: 33%; DES: 60%), while in the case of the classic form, it does not change much when analysing the time intervals (6–12 months: 14.5%; 12–24 months: 20.8%; >24 months: 18.7%). We may thus conclude that, in certain cases, the increased tone of the oesophagus may extend well above the level of the LES, where conventional and a properly performed myotomy cannot always reach.

The other myotomy-related complaint is the development of GERD. Based on observations by Campos and other authors, reflux occurs in 41.5% without an antireflux procedure and only in 14.5% with one, thus confirming that if the LES, the main barrier, is damaged, reflux may be expected (73,87). By completing the procedure with partial fundoplication, the occurrence of postoperative reflux can be decreased considerably, without increasing the pressure of the LES. Both anterior (Dor, 180°) and posterior (Toupet, 270°) semifundoplication is widely used after a cardiomyotomy. There is an argument between supporters of Dor and Toupet as to which fundoplication is better. Experts in favour of Dor argue that anterior fundoplication is easier to perform and non-dissection of the posterior part of the oesophagus may help against GER. However, supporters of Toupet state it may keep the edges of the myotomy separated, reducing the probability of recurrent dysphagia and diminishing development of GERD. Comparing these two methods, there were no significant differences between the three RCT trials and their meta-analysis with regard to postoperative dysphagia and GERD (88-93, Table 9). Their use is thus basically determined by the preference of the surgical team. In a recent, large prospective clinical trial, laparoscopic Heller–Dor procedure has proved to be successful as regards acceptable low morbidity (4.7%) and durable symptom control (89.5%) in the long term in 1001 achalasia patients (93).

Based on our results, it is clear that the rate of GERD after a Heller–Dor procedure was minimal (6.2%, 3/48) in the medium term (24-month follow-up) and was controlled with conservative therapy.

Megaoesophagus

The risk of oesophageal cancer is increased by long-lasting achalasia, marked oesophageal dilation and mucus congestion (94-95).

The best way to prevent cancer is timely treatment – primarily surgical therapy. If a cardiomyotomy is performed late, that is, after a sigmoid deformity of the oesophagus has developed, effective cancer prevention can no longer be achieved; what is more, the results of radical surgery are also unsatisfactory because of the late recognition (96-97).

In the megaoesophagus stage, the risk of aspiration pneumonia, malignant transformation and malnutrition is markedly high, the majority of patients have undergone innumerable endoscopic and/or surgical procedures, and indications for surgery are continuously recurrent symptoms

and the sigmoid deformity of the oesophagus. The morbidity rate for radical intervention varies between 19 and 50%, with the most common complications being pneumonia and anastomotic leak. The mortality rate is between 0 and 5.4%, the length of stay is between ten and 16 days, and slightly more than one-quarter of patients will later require endoscopic balloon dilation for anastomotic stricture (98). All our patients scheduled for elective resection had an afunctional, significantly dilated oesophagus, and their number (3/54, 5%) corresponded to the literature data. Great care was taken to individualize the type of surgery during surgical treatment, and this decision was made by the surgical team with experience of oesophageal surgery after considering the patient's physical condition, the intraoperative characteristics and the long-term optimal quality of life. In the case of reconstruction, all three eligible organs were used (stomach, jejunum and colon), neither an anastomotic leak nor pneumonia was observed after the interventions, and there was no mortality. The swallowing function of these patients is now satisfactory, and no anastomotic stricture or other complications were found during the follow-up visits.

It was long maintained that the only surgical treatment possible for megaoesophagus is oesophageal resection, with stomach, jejunum or colon used as a replacement (99). Because of the surgical burden and the relatively high rate of perioperative morbidity, a cardiomyotomy, which may result in symptomatic improvement, could become prevalent in high-risk cases. A number of authors have reported a noticeable improvement in symptoms even in these decompensated patients with sigmoid oesophagus (100-103). Both postoperative functional assessments of the patients and quality-of-life questionnaires confirm the justification and usefulness of a myotomy. Mineo's team performed a Heller myotomy in 14 achalasia patients with sigmoid deformity of the oesophagus. After 85 months of follow-up, the result was excellent or good in 72% of the cases, while the postoperative dysphagia and regurgitation scores significantly decreased and matched those observed in achalasia patients operated on in the early stage (100). In patients undergoing surgery for megaoesophagus, numerous publications have confirmed the efficacy of LHM in achieving postoperative symptom control, and resection was not necessary in any of the patients as a result of a persistently good quality of life (102-103).

The fact that LHM is not always effective in the treatment of sigmoid oesophagus was demonstrated by Zaninotto et al. in their analysis of more than 400 cases involving a myotomy for oesophageal achalasia. At the end of their long-term, prospective study, they concluded that a high preoperative LES pressure has a beneficial effect on the outcome of the surgery, while a

stage IV (sigmoid) oesophagus has an adverse effect. Radical oesophagectomy is often unavoidable because of the persistent symptoms, but, after informing the patient properly, a minimally invasive myotomy is worth pursuing as a first step in the hope of a positive response to therapy (79). In our own patient population, a young woman with sigmoid oesophagus underwent LHM after multiple unsuccessful endoscopic dilations, and satisfactory swallowing function was observed for almost six months. However, since dysphagia returned after the complaint-free period, oesophageal resection with jejunal interposition (the Merendino procedure) was performed. At present, after more than a decade of follow-up, the patient is completely symptom-free, her swallowing is unrestricted, and her quality of life is excellent.

Postendoscopic oesophageal injury

In large centres, a perforation rate of about 1%, as detailed above, should be expected while the patient is treated with EBD as non-surgical treatment of achalasia. Performing the intervention on a prepared patient and timely recognition of the lesion by an experienced gastroenterologist are important factors in the patient's emergency surgery. The mortality rate for oesophageal perforation ranges between 18 and 22% – even despite early recognition and treatment. If the time elapsed between injury and surgery exceeds 24 hours, the mortality rate may even reach 27 to 40% (104). In the case of oesophageal injury, a personalized treatment strategy is required in each case, and the following factors should be taken into account: aetiology of the injury, existing underlying oesophageal disease, time from injury to diagnosis, septic condition, comorbidities and physical capacity (105). Post-EBD oesophageal perforations are traditionally treated surgically, but therapeutic methods also include conservative treatment and modern endoscopic techniques (OTSC clip and stent implantation) (106-109).

Basically, early surgical treatment is required for larger lesions that cannot be treated endoscopically in the case of a contrast agent leak into the pleural and/or peritoneal space. Many authors agree that a similar decision is warranted with the involvement of a surgeon as soon as possible even for smaller lesions (110). Time elapsed since a perforation has a considerable effect on the success of the surgery, although there is experience with both early and later (>24 hours) successful laparoscopic primary closures in the literature (110-111). In our practice, primary suture repair is used in cases that are recognised early, within 24 hours, and it is always completed with the cardiomyotomy and antireflux procedure, which has a beneficial

effect on the healing of the lesion and, at the same time, may result in long-term symptom-free status.

In the case of perforations beyond 24 hours, patients usually undergo resection without reconstruction (on rare occasion, with immediate reconstruction) because of the septic condition that has developed and the reduced tendency of the oesophageal wall to heal. In the case of megaoesophagus, a worse-than-average condition of the oesophagus supports resection, which is worth including during surgical treatment in all cases. In tertiary centres with experience of oesophageal resection, mortality rates similar to that of primary suture repair can be achieved (17% [0–43%] vs. 12% [0–31%]) (112-113). The importance of a multidisciplinary approach and a correctly chosen treatment strategy is highlighted by a study conducted at our department, which summarized cases of spontaneous oesophageal perforation and demonstrated an acceptably low mortality rate (6.6%) owing to timely and well-executed procedures (114).

Every patient in our acute surgery group was admitted to our unit for an oesophagoscopy-associated injury. In the two early cases (recognised within 24 hours), primary suture repair occurred with Heller–Dor surgery, taking the condition of the patients into account, while oesophageal resection without reconstruction was performed in the two other cases with an old perforation complicated by megaoesophagus. There was no mortality or notable morbidity in the emergency group.

6. CONCLUSION

(1) According to our study, both TCD and TSD procedures are safe operations for Zenker's diverticula. The transoral approach has all the advantages offered by a minimally invasive manner, but is optimal primarily in the setting of a mid-sized diverticulum (3–6 cm). We can expect a significant quality of life improvement after the procedures, but recurrent symptoms may be developed in a certain proportion of patients. Our working group was among the first to employ the transoral stapler diverticulostomy as an innovative method in the management of Zenker's diverticulum in a study involving the largest cohort in this topic area in Hungary with both short- and long-term results.

(2) Based on our results, similarly to the literature data, it may be established that laparoscopic-transhiatal epiphrenic diverticulum resection with the Heller–Dor procedure can be considered a safe surgical procedure with low morbidity and satisfying long-term outcomes. Myotomy and antireflux surgery are essential for lasting and reliable clinical success. Our working group was the first to publish short- and long-term results of a new minimally invasive method in Hungary.

(3) As reported in our comprehensive research, laparoscopic Heller–Dor surgery is a safe and effective surgical method for treating oesophageal achalasia. Symptom control in patients who have undergone minimally invasive surgery is adequate even in the long term, and the rate of postoperative reflux is low. However, patients with the spastic type may develop recurrent symptoms at a higher rate. Advanced and emergency conditions are still a major challenge for surgeons, and choosing the proper therapeutic strategy depends on several factors. On the whole, surgery for achalasia is only recommended in institutions where every aspect of the condition can be managed effectively and reliably.

7. ACKNOWLEDGEMENTS

I wish to express my deep and sincere gratitude to my supervisor, **Dr. György Lázár**, Professor and Head of the Department of Surgery, University of Szeged, for giving me the opportunity to conduct research and providing invaluable guidance throughout. His immense knowledge, vision, sincerity and motivation have deeply inspired me. It has been a great privilege and honour to work and study under his guidance.

I would like to offer my special thanks to my research colleagues, **Dr. Attila Paszt, Dr. Zsolt Simonka** and **Dr. Szabolcs Ábrahám,** for their assistance and encouragement at every stage of the research project, as well as to **Dr. Márton Erdős** for his help with the data analysis.

I wish to extend my thanks to **Dr. András Rosztóczy** and **Dr. Georgina Ollé**, and all the members of the motility group at the 1st Department of Internal Medicine, University of Szeged, for their genuine support and harmonious collaboration throughout this research.

I would also like to acknowledge **Dr. László Rovó**, Professor and Head of the Department of Oto-Rhino-Laryngology and Head-Neck Surgery, University of Szeged, as a co-author of the Zenker's diverticulum study for his very valuable comments.

Thanks go to **Andrea Vida** as well for her kindness and technical support in my studies.

Thank you as well to all the people at the Department of Surgery, University of Szeged, who have directly or indirectly supported me in completing the research .

I am extremely grateful to my parents for their love, caring and sacrifices in educating and preparing me for my future. I am very thankful to my wife and my children for their love, understanding and continuing support as I completed this research.

REFERENCES

1. Watemberg S, Landau O, Avrahami R. Zenker's diverticulum: reappraisal. Am J Gastroenterol. 1996; 91: 1494–1498.
2. Lord RV, DeMeester TR, Theisen J, Peters JH, Crookes PF, Bremner CG. Physiologic basis for the treatment of epiphrenic diverticulum. Ann Surg. 2002;3:346 –354.
3. Melman L, Quinlan J, Robertson B, et al. Esophageal manometric characteristics and outcomes for laparoscopic esophageal diverticulectomy, myotomy, and partial fundoplication for epiphrenic diverticula. Surg Endosc. 2009;23:1337–1341.
4. Del Genio A, Rossetti G, Maffetton V, et al. Laparoscopic approach in the treatment of epiphrenic diverticula: long-term results. Surg Endosc. 2004;18:741–745.
5. Varghese TK Jr, Marshall B, Chang AC, Pickens A, Lau CL, Orringer MB. Surgical treatment of epiphrenic diverticula: a 30-year experience. Ann Thorac Surg. 2007;84:1801–1809.
6. Altorki NK, Sunagawa M, Skinner DB. Thoracic esophageal diverticula: why is operation necessary? J Thorac Cardiovasc Surg. 1993;105:260 –264.
7. Benacci JC, Deschamps C, Trastek VF, Allen MS, Daly RC, Pairolero PC. Epiphrenic diverticulum: results of surgical treatment. Ann Thorac Surg. 1993;55:1109 –1113.
8. Jordan PH Jr, Kinner BM. New look at epiphrenic diverticula. World J Surg. 1999;23:147–152.
9. Castrucci G, Porziella V, Granone PL, Picciocchi A. Tailored surgery for esophageal body diverticula. Eur J Cardiothorac Surg. 1998;14:380 –387.
10. Klaus A, Hinder RA, Swain J, Achem SR. Management of epiphrenic diverticula. J Gastrointest Surg. 2003;7:906 –911.
11. Herbella FA, Patti MG. Modern pathophysiology and treatment of esophageal diverticula. Langenbecks Arch Surg. 2012; 397:29 –35.
12. Krill JT, Naik RD, Vaezi MF. Clinical management of achalasia: current state of the art. Clin Exp Gastroenterol. 2016; 9: 71-82.
13. Moonen A, Boeckxstaens G. Current diagnosis and management of achalasia. J Clin Gastroenterol. 2014; 48: 484-490.
14. Sadowski DC, Ackah F, Jiang B, et al. Achalasia: incidence, prevalence and survival: a population based study. Neurogastroenterol Motil. 2010; 22: e256-e261.
15. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015; 27: 160-174.
16. Mosher H. Webs and pouches of the oesophagus, their diagnosis and treatment. Surg Gynecol Obstet. 1917; 25: 175–187.
17. Dohlman G, Mattsson O. The endoscopic operation for hypopharyngeal diverticula: a roentgencinematographic study. AMA Arch Otolaryngol. 1960; 71: 744–752.
18. Collard JM, Otte JB, Kestens PJ. Endoscopic stapling technique of esophagodiverticulostomy for Zenker's diverticulum. Ann Thorac Surg. 1993; 56: 573–576.
19. Lázár G, Rovó L, Szentpáli K, et al. Endoscopic stapling diverticulostomy for Zenker's diverticulum. [Endoszkópos varrógéppel képzett diverticulostoma a Zenker-diverticulum kezelésére.] Orv Hetil. 2004; 145: 15–17. [Hungarian]
20. Thomas ML, Anthony AA, Fosh BG, Finch JG, Maddern GJ. Esophageal diverticula. Br J Surg. 2001;88:629 – 642.
21. Shimi S, Nathanson LK, Cuschieri A. Laparoscopic cardiomyotomy for achalasia. J R Coll Surg Edinb. 1991; 36: 152-154.
22. Pellegrini C, Wetter LA, Patti M, et al: Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. Ann Surg 1992; 216: 291-296.
23. Eckardt VF, Gockel I, Bernhard G. Pneumatic dilation for achalasia: late results of a prospective follow up investigation. Gut. 2004;535:629 – 633

24. Zaninotto G, Portale G, Costantini M, Merigliano S, Guirroli E, Rissetto C. Long-term outcome of operated and unoperated epiphrenic diverticula. J Gastrointest Surg. 2008;12:1485–1490.
25. Ozgursoy OB, Salassa JR. Functional and manofluorographic outcomes after transoral endoscopic pharyngesophageal diverticulostomy. Arch Otolaryngol Head Neck Surg. 2010; 136: 463–467.
26. Yuan Y, Zhao YF, Hu Y, et al. Surgical treatment of Zenker's diverticulum. Dig Surg. 2013; 30: 207–218.
27. Chang CY, Payyapilli RJ, Scher RL, et al. Endoscopic staple diverticulostomy for Zenker's diverticulum: review of literature and experience in 159 consecutive cases. Laryngoscope 2003; 113: 957–965.
28. Yip HT, Leonard R, Kendall KA. Cricopharyngeal myotomy normalizes the opening size of the upper esophageal sphincter in cricopharyngeal dysfunction. Laryngoscope 2006; 116: 93–96.
29. Skinner KA, Zuckerbraun L. Recurrent Zenker's diverticulum: treatment with crycopharyngeal myotomy. Am Surg. 1998; 64: 192–195.
30. Wilken R, Whited C, Scher RL. Endoscopic staple diverticulostomy for Zenker's diverticulum: review of experience in 337 cases. Ann Otol Rhinol Laryngol. 2015; 124: 21–29.
31. Shahawy S, Janisiewicz AM, Annino D, et al. A comparative study of outcomes for endoscopic diverticulotomy versus external diverticulectomy. Otolaryngol Head Neck Surg. 2014; 151: 646–651.
32. Verdonck J, Morton RP. Systematic review on treatment of Zenker's diverticulum. Eur Arch Otorhinolaryngol. 2015; 272: 3095–3107.
33. Chang CW, Burkey BB, Netterville JL, et al. Carbon dioxide laser endoscopic diverticulotomy versus open diverticulectomy for Zenker's diverticulum. Laryngoscope 2004; 114: 519–527.
34. Bonavina L, Rottoli M, Bona D, et al. Transoral stapling for Zenker's diverticulum: effect of the traction suture-assisted technique on long-term outcomes. Surg Endosc. 2012; 26: 2856–2861.
35. Mulder CJ, den Hartog G, Robijn RJ, et al. Flexible endoscopic treatment of Zenker's diverticulum: a new approach. Endoscopy 1995; 27: 438–442.
36. Ishioka S, Sakai P, Maluf Filho F, et al. Endoscopic incision of Zenker's diverticula. Endoscopy 1995; 27: 433–437.
37. Ferreira LE, Simmons DT, Baron TH. Zenker's diverticula: pathophysiology, clinical presentation, and flexible endoscopic management. Dis Esophagus 2008; 21: 1–8.
38. Case DJ, Baron TH. Flexible endoscopic management of Zenker's diverticulum: the Mayo Clinic experience. Mayo Clin Proc. 2010; 85: 719–722.
39. Dzeletovic I, Ekbom DC, Baron TH. Flexible endoscopic and surgical management of Zenker's diverticulum. Expert Rev Gastroenterol Hepatol. 2012; 6: 449–466.
40. Gyökeres T. Endoscopic treatment of Zenker's diverticulum. [Zenker-diverticulum endoszkópos kezelése.] ESGE Days 2018, Budapest, 2018. április 19. [Kongresszusi előadás] [Hungarian]
41. Antonello A, Ishaq S, Zanatta L, et al. The role of flexible endotherapy for the treatment of recurrent Zenker's diverticula after surgery and endoscopic stapling. Surg Endosc. 2016; 30: 2351– 2357.
42. Seth R, Rajasekaran K, Lee WT, et al. Patient, reported outcomes in endoscopic and open transcervical treatment for Zenker's diverticulum. Laryngoscope 2014; 124: 119–125.
43. Johnson CM, Postma GN. Zenker's diverticulum – which surgical approach is superior? JAMA Otolaryngol Head Neck Surg. 2016; 142: 401–403.
44. Soares RV, Montenovo M, Pellegrini CA, Oelschlager BK. Laparoscopy as the initial approach for epiphrenic diverticula. Surg Endosc. 2011;25:3740 –3746.
45. Silecchia G, Casella G, Recchia CL, Bianchi E, Lomartire N. Laparoscopic transhiatal treatment of large epiphrenic esophageal diverticulum. JSLS. 2008;12(1):104 –108.

46. Fekete F, Vonns C. Surgical management of esophageal thoracic diverticula. Hepatogastroenterology. 1992;39:97–99.
47. Zaninotto G, Portale G, Costantini M, Zanatta L, Salvador R, Ruol A. Therapeutic strategies for epiphrenic diverticula: systematic review. World J Surg. 2011;35:1447–1453.
48. Tedesco P, Fisichella PM, Way LW, Patti MG. Cause and treatment of epiphrenic diverticula. Am J Surg. 2005;190:891– 894.
49. Fernando HC, Luketich JD, Samphire J, et al. Minimally invasive operation for esophageal diverticula. Ann Thorac Surg. 2005;80:2076 –2080.
50. Rosati R, Fumagalli U, Bona S, et al. Laparoscopic treatment of epiphrenic diverticula. J Laparoendosc Adv Surg Tech A. 2001;11:371–375.
51. Palanivelu C, Rangarajan M, John SJ, Parthasarathi R, Senthilkumar R. Laparoscopic transhiatal approach for benign supra-diaphragmatic lesions of the esophagus: a replacement for thoracoscopy? Dis Esophagus. 2008;21:176 –180.
52. Allaix ME, Borraez Segura BA, Herbella FA, Fisichella PM, Patti MG. Is resection of an esophageal epiphrenic diverticulum always necessary in the setting of achalasia? World J Surg. 2015; 39:203–207.
53. Rossetti G, Fei L, del Genio G, et al. Epiphrenic diverticula mini-invasive surgery: a challenge for expert surgeons: personal experience and review of the literature. Scand J Surg. 2013;102: 129 –135.
54. Rosati R, Fumagalli U, Elmore U, de Pascale S, Massaron S, Peracchia A. Long-term results of minimally invasive surgery for symptomatic epiphrenic diverticulum. Am J Surg. 2011;201:132– 135.
55. Zaninotto G, Parise P, Salvador R, et al. Laparoscopic repair of epiphrenic diverticulum. Semin Thorac Cardiovasc Surg. 2012;24:218 –222
56. Bowman TA, Sadowitz BD, Ross SB, Boland A, Luberice K, Rosemurgy AS. Heller myotomy with esophageal diverticulectomy: an operation in need of improvement. Surg Endosc. 2016; 30:3279 –3288
57. Heller E. Extramukose cardiaplastik beim chronischen cardiospasmus mit dilatation des oesophagus. Mitt Grenzgeb Med Chir. 1913; 27: 141-149.
58. Zaaijer JH. Cardiospasm in the aged. Ann Surg. 1923; 77: 615-617.
59. Olah T, Szendrényi V, Wittmann T, et al. Treatment of achalasia of the cardia using thoracoscopic esophago-myotomy. Orv Hetil. 1997; 138: 11-13.
60. Andrási L, Paszt A, Simonka Z, et al. Laparoscopic surgery for epiphrenic esophageal diverticulum. JSLS. 2018; e2017.00093. doi: 10.4293/JSLS.2017.00093.
61. Andrási L, Ábrahám S, Simonka Z, et al. A comparative study of short- and long-term outcomes for transcervical versus transoral surgery for Zenker's diverticulum. Orv Hetil. 2019; 160: 629-635.
62. Simonka Z, Paszt A, Abrahám S, et al. The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. Scand J Gastroenterol. 2012; 47: 13-21.
63. Lázár G, Szentpáli K, Szántó I, et al. Successful thoracoscopic surgical treatment of esophageal cyst. Acta Chir Hung. 1999; 38: 191-192.
64. Lázár G, Oláh T, Szendrényi V, et al. Successful videothoracoscopic surgical treatment of esophageal cyst and leiomyoma Magy. Seb. 1999; 52: 113-116.
65. Gelfond M, Rozen P, Gilat T. Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. Gastroenterology. 1982; 83: 963-969.
66. Pasricha PJ, Rai R, Ravich WJ, et al. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology. 1996; 110: 1410-1415.
67. Smith CD, Stival A, Howell DL, et al. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. Ann Surg. 2006; 243: 579-584.
68. Hulselmans M, Vanuytsel T, Degreef T, et al. Long-term outcome of pneumatic dilation in the treatment of achalasia. Clin Gastroenterol Hepatol. 2010; 8: 30e35.

69. Lynch KL, Pandolfino JE, Howden CW, et al. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic eview of the literature. Am J Gastroenterol. 2012; 107: 1817-1825.
70. Boeckxstaens GE, Annese V, Varannes SB des, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. N Engl J Med. 2011; 364: 1807-1816.
71. Moonen A, Annese V, Belmans A, et al. Longterm results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. Gut. 2016; 65: 732-739.
72. Persson J, Johnsson E, Kostic S, et al. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: long-term results of a prospective, randomized study. World J Surg 2015; 39: 713-720.
73. Campos GM, Vittinghoff E, Rabl C, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg. 2009; 249: 45e57.
74. Yaghoobi M, Mayrand S, Martel M, et al. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. Gastrointest Endosc. 2013; 9: 468-475.
75. Schoenberg MB, Marx S, Kersten JF, et al. Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. Ann Surg 2013; 258: 943-952.
76. Oude Nijhuis RAB, Prins LI, Mostafavi N, et al. Factors associated with achalasia treatment outcomes: Systematic review and meta-analysis. Clin. Gastroenterol. Hepatol. DOI: 10.1016/j.cgh.2019.10.008.
77. Costantini A, Familiari P, Costantini M, et al. Poem versus laparoscopic Heller myotomy in the treatment of esophageal achalasia: a case-control study from two high volume centers using the propensity score. J Gastrointest Surg. 2020; 24: 505–515.
78. Werner YB, Hakanson B, Martinek J et al. Endoscopic or surgical myotomy in patients with idiopathic achalasia. N Engl J Med. 2019; 381: 2219–2229.
79. Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment for achalasia depend on manometric subtye. Gastroenterology. 2013; 144: 718e725.
80. Ngamruengphong S, Inoue H, Chiu PW, et al. Long-term outcomes of per-oral endoscopic myotomy in patients with achalasia with a minimum follow-up of 2 years: an international multicenter study. Gastrointest Endosc 2017; 85: 927-933.e2.
81. Ancona E, Anselmino M, Zaninotto G. Et al. Esophageal achalasia: laparoscopic versus conventional open Heller-Dor operation. Am J Surg. 1995; 170: 265-270.
82. The 2018 ISDE achalasia guidelines. Dis Esophagus. 2018 Sep 1;31(9). doi: 10.1093/dote/doy071.
83. Mattioli S, Pilotti V, Felice V, et al. Intraoperative study on the relationship between the lower esophageal sphincter pressure and the muscular components of the gastro-esophageal junction in achalasic patients. Ann Surg. 1993; 218: 635-639.
84. Oelschlager BK, Chang L, Pellegrini C A. Improved outcome after extended gastric myotomy for achalasia. Arch Surg. 2003; 138: 490-495; discussion 5–7.
85. Teitelbaum EN, Soper NJ, Pandolfino JE, et al. An extended proximal esophageal myotomy is necessary to normalize EGJ distensibility during Heller myotomy for achalasia, but not POEM. Surg Endosc. 2014; 28: 2840-2487.
86. Horváth ÖP, Lázár G. Failed operations for achalasia. Dis Esophagus. 1991; 4: 149-153.
87. Richards WO, Torquati A, Holzman MD, et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg. 2004; 240: 405-412.
88. Kumagai K, Kjellin A, Tsai JA, et al. (2014) Toupet versus Dor as a procedure to prevent reflux after cardiomyotomy for achalasia: results of a randomised clinical trial. Int J Surg. 2014; 12: 673-680.

89. Torres-Villalobos G, Coss-Adame E, Furuzawa-Carballeda et al. Dor versus Toupet fundoplication after laparoscopic Heller myotomy: long-term randomized controlled trial evaluated by high-resolution manometry. J Gastrointest Surg. 2018; 22: 13-22.
90. Rawlings A, Soper NJ, Oelschlager B, et al. Laparoscopic Dor versus Toupet fundoplication following Heller myotomy for achalasia: results of a multicenter, prospective, randomized-controlled trial. Surg Endosc. 2012; 26: 18-26.
91. Siddaiah-Subramanya M, Yunus RM, Khan S, et al (2019) Anterior Dor or posterior Toupet with Heller myotomy for achalasia cardia: A systematic review and meta-analysis. World J Surg. 2019; 43: 1563-1570.
92. Rebecchi F, Giaccone C, Farinella E, et al. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia: long-term results. Ann Surg. 2008;248(6):1023–30.
93. Costantini M, Salvador R, Capovilla G, et al. Thousand and one laparoscopic Heller myotomies for esophageal achalasia: a 25-year experience at a single tertiary center. J Gastrointest Surg. 2019; 23: 23-35.
94. Leeuwenburgh I, Scholten P, Alderliesten J, et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. Am J Gastroenterol. 2010; 105: 2144-2149.
95. Tustumi F, Bernardo WM, da Rocha JRM, et al. Esophageal achalasia: a risk factor for carcinoma. A systematic review and meta-analysis. Dis Esophagus. 2017; 30: 1-8.
96. Orringer MB, Orringer JS. Esophagectomy: definitive treatment for esophageal neuromotor dysfunction Ann Thorac Surg 1982; 34: 237–248. doi: 10.1016/s0003-4975(10)62492-7.
97. Zaĭtsev VT, Dalavurak VT, Kuznetsov AV, Kudinenko AS. State of the esophageal mucosa in cardiospasm Klin Khir. 1979; 10: 45-49.
98. Aiolfi A, Asti E, Bonitta G, et al. Esophageal Resection for End-Stage Achalasia. Am Surg. 2018; 84: 506-511.
99. Watson TJ. Esophagectomy for end-stage achalasia. World J Surg. 2015; 39: 1634-1641.
100. Mineo TC, Pompeo E. Long-term outcome of Heller myotomy in achalasic sigmoid esophagus. J Thorac Cardiovasc Surg 2004; 128: 402-407.
101. Faccani E, Mattioli S, Lugaresi ML, et al. Improving the surgery for sigmoid achalasia: long-term results of a technical detail. Eur J Cardiothorac Surg 2007; 32: 827-833.
102. Sweet MP, Nipomnick I, Gasper WJ, et al. The outcome of laparoscopic Heller myotomy for achalasia is not influenced by the degree of esophageal dilatation. J Gastrointest Surg 2008; 12: 159-165.
103. Panchanatheeswaran K, Parshad R, Rohila J, et al. Laparoscopic Heller's cardiomyotomy: a viable treatment option for sigmoid oesophagus. Interact Cardiovasc Thorac Surg 2013; 16: 49-54.
104. Sandrasagra FA, English TAH, Milstein BB. The management and prognosis of esophageal perforation. Br J Surg 1978; 65: 629-632.
105. White RK, Morris DM. Diagnosis and management of esophageal perforations. Am Surg 1992; 58: 112-119.
106. Brinster CJ, Singhal S, Lee L, et al. Evolving options in the management of esophageal perforation. Ann Thorac Surg 2004; 77: 1475-1483.
107. Vanuytsel T, Lerut T, Coosemans W, et al. Conservative management of esophageal perforations during pneumatic dilation for idiopathic esophageal achalasia. Clin Gastroenterol Hepatol. 2012; 10: 142-149.
108. Sanaka MR, Raja S, Thota PN. Esophageal Perforation After Pneumatic Dilation for Achalasia: Successful Closure With an Over-the-Scope Clip. J Clin Gastroenterol. 2016; 50: 267-268.
109. Elhanafi S, Othman M, Sunny J, et al. Esophageal perforation post pneumatic dilatation for achalasia managed by esophageal stenting. Am J Case Rep. 2013; 14: 532-535. doi: 10.12659/AJCR.889637. eCollection 2013.

110. Ghoshal UC, Karyampudi A, Verma A, et al. Perforation following pneumatic dilation of achalasia cardia in a university hospital in northern India: A two-decade experience. Indian J Gastroenterol. 2018; 37: 347-352. doi: 10.1007/s12664-018-0874-5. Epub 2018 Aug 18.
111. Sánchez-Pernaute AI, Aguirre EP, Talavera P, et al. Laparoscopic approach to esophageal perforation secondary to pneumatic dilation for achalasia. Surg Endosc. 2009; 23: 1106-1109. doi: 10.1007/s00464-008-0114-7. Epub 2008 Sep 24.
112. Urbani M, Mathisen DJ. Repair of esophageal perforation after treatment for achalasia. Ann Thorac Surg. 2000; 69: 1609-1611.
113. Sudarshan M, Elharram M, Spicer J, et al. Management of esophageal perforation in the endoscopic era: Is operative repair still relevant? Surgery. 2016; 160: 1104-1110. doi: 10.1016/j.surg.2016.07.025. Epub 2016 Aug 11.
114. Lázár G, Paszt A, Mán E. Role of endoscopic clipping in the treatment of esophageal perforations. World J Gastrointest Endosc. 2016; 8: 13-22. doi: 10.4253/wjge.v8.i1.13.