MINIMALLY INVASIVE SURGICAL PROCEDURES IN THE TREATMENT OF BARRETT'S ESOPHAGUS

Zsolt Simonka M D

Ph D Thesis

2016

Szeged

MINIMALLY INVASIVE SURGICAL PROCEDURES IN THE TREATMENT OF BARRETT'S ESOPHAGUS

Zsolt Simonka M D

Ph D Thesis

UNIVERSITY OF SZEGED FACULTY OF MEDICINE
DEPARTMENT OF SURGERY

DOCTORAL SCHOOL OF CLINICAL MEDICINE

SUPERVISOR
Prof. György Lázár M D, Ph D, D Sc

2016

Szeged

CONTENTS

LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. **Simonka Zs, Paszt A, Ábrahám Sz, Pieler J, Tajti J, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Rárosi F, Lázár Gy:** The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. *Scand J Gastroenterol* 47:13-21, 2012. IF: 2,019

II. **Simonka Zs, Paszt A, Géczi T. Ábrahám Sz, Tóth I, Horváth Z, Pieler J, Tajti J, Varga Á, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy:** Refluxbetegség és Barrett-nyelőcső miatt műtétre kerülő betegek összehasonlító vizsgálata. Comparison of surgical patients with gastroesophageal reflux disease and Barrett's esophagus. *Magy Seb* 67:287–296, 2014.

III. **Rokszin R, Simonka Z, Paszt A, Szepes A, Kucsa K, Lazar G.** Successful endoscopic clipping in the early treatment of spontaneous esophageal perforation. *Surg Lapar Percutan Tech* 21: e311-e31, 2011. IF: 1,227

IV. **Lázár G Jr, Paszt A, Simonka Z, Bársony A, Abrahám S, Horváth G.** A successful strategy for surgical treatment of Boerhaave's syndrome. *Surg Endosc* 25:3613-9, doi: 10.1007/s00464-011-1767-1. Epub Jun 11, 2011.
IF: 4,013

LIST OF ABSTRACTS RELATED TO THE SUBJECT OF THE THESIS

I. **Simonka Zs, Paszt A, Géczi T, Ábrahám Sz, Tóth I, Horváth Z, Pieler J, Tajti J, Varga Á, Lup M, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Barrett nyelőcső miatt végzett antireflux műtét hosszú távú eredményei. In: *Magyar Sebész Társaság Sebészeti Endoszkópos Szekció XVI. Kongresszusa Sebészeti Továbbképző Tanfolyam*. Eger, 2015. november 12 -14. Eger: p. 100.

II. **G Lazar, Zs Simonka, A Paszt, Sz Abraham, J Pieler, J Tajti, L Tiszlavicz, I Nemeth, F Izbeki, A Rosztoczy, F Rarosi.** The effects of laparoscopic Nissen fundoplication on Barret's esophagus: longterm results. *Surg Endosc* 26:(Suppl. 1.) p. S38, 2012.

III. **Lázár Gy, Paszt A, Ábrahám Sz, Pieler J, Tajti J, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Rárosi F, Simonka Zs**. The effects of laparoscopic Nissen fundoplication on Barrett's esophagus:: long-term results. *Dis Esophagus* 25:(S1) Paper P01.07, 2012.

IV. **Rokszin R, Simonka Zs, Paszt A, Szepes A, Kucsa K, Lázár Gy.** A spontán nyelőcső-perforatio korai ellátása endoscopos klippeléssel. *Magy Seb* 65:314-315, 2012.

V. **Simonka Zs, Paszt A, Ábrahám Sz, Bársony A, Horváth G, Lázár Gy.** A Boerhaave-syndroma sebészi kezelésének stratégiája. *Magy Seb* 65:270-271, 2012.

VI. **Simonka Zs, Paszt A, Géczi T, Ábrahám Sz, Pieler J, Tajti J, Izbéki F, Rosztóczy A, Wittmann T, Tiszlavicz L, Németh I, Lázár Gy.** A laparoscopos antireflux műtét szerepe a Barrett-nyelőcső sebészi kezelésében. *Magy Seb* 64:163, 2011.

VII. **Lázár Gy, Paszt A, Simonka Zs, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T.** The effect of laparoscopic Nissen fundoplication on Barrett's esophagus and GERD. *Dis Esophagus* 23:(Suppl.1) 59A, 2010.

VIII. **Simonka Zs, Paszt A, Géczi T, Ábrahám Sz, Pieler J, Tajti J, Izbéki F, Rosztóczy A, Wittmann T, Tiszlavicz L, Németh I, Lázár Gy.** A laparoscopos antireflux műtét szerepe a Barrett nyelőcső sebészi kezelésében. *Magy Seb* 63:237-238, 2010.

IX. **Simonka Zs, Paszt A, Géczi T, Ábrahám Sz, Pieler J, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, ifj Lázár Gy.** The role of antireflux surgery in the treatment of Barrett's esophagus. *Z Gastroenterol* 48:615, 2010.

X. **Simonka Zs, Paszt A, Ábrahám Sz, Géczi T, Pieler J, Tajti J, Mészáros P, Dargai S, Horváth Z, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Efficiency of laparoscopic procedure in Barrett's esophagus. *Nihon Geka Gakkai Zasshi* 111:(suppl.2) p. 263, 2010.

XI. **Simonka Zs, Paszt A, Ábrahám Sz, Géczi T, Tóth I, Horváth Z, Pethő I, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Comparison of efficiency of laparoscopic procedures in GERD and Barrett's esophagus (short term functional and histological results). *Br J Surg* 96:(Suppl.5) 55-56, 2009.

XII. **Simonka Z, Paszt A, Géczi T, Ábrahám S, Tóth I, Horváth Z, Pethő I, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár G.** Comparison of efficiency of laparoscopic procedures in GERD and Barrett's esophagus. *Z Gastroenterol* 46:510-511, 2008.

XIII. **Simonka Zs, Paszt A, Ábrahám Sz, Géczi T, Tóth I, Horváth Z, Pethő I, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Comparison of efficiency of laparoscopic procedures in GERD and Barrett's esophagus (short term functional and histological results). *Hepatogastroenterology* 55:(Suppl.1) A186, 2008.

XIV. **Simonka Zs, Paszt A, Ábrahám Sz, Pethő I, Tiszlavicz L, Németh I, Izbéki F, Rocztóczy A, Wittmann T, Lázár Gy.** Laparoscopos antireflux műtét szerepe a Barrett-nyelőcső kezelésében. *Magy Seb* 61:187, 2008.

XV. **Simonka Zs, Paszt A, Ábrahám Sz, Pethő I, Tiszlavicz L, Németh I, Izbéki F, Rocztóczy A, Wittmann T, Lázár Gy.** Laparoscopos antireflux műtét szerepe a Barrett-nyelőcső kezelésében. *In: A Magyar Sebész Társaság 59. Kongresszusa: Sebészeti Továbbképző Tanfolyam. Debrecen, 2008. június 18-20.* Paper 143.

ABBREVIATIONS

BE, Barrett's esophagus

BMI, body mass index

CM, cardiac metaplasia

COX-2, cyclooxygenase-2

D, dysplastic (group)

ERD, erosive reflux disease

FM, fundic metaplasia

GERD, gastroesophageal reflux disease

GEJ, gastroesophageal junction

HGD, high-grade dysplasia

I, intestinal (group)

IH, immunohistochemistry

IM, intestinal metaplasia

LES, lower esophageal sphincter

LGD, low-grade dysplasia

lLES, length of lower esophageal sphincter

LSBE, long-segment Barrett's esophagus

NBI, narrow band imaging

NERD, non-erosive reflux disease

NI, non-intestinal (group)

pLES, pressure of lower esophageal sphincter

PPI, proton-pump inhibitor

PTFE, polytetrafluoroethylene

PTX, pneumothorax

rLES, relaxation time of lower esophageal sphincter

SD, standard deviation

SSBE, short-segment Barrett's esophagus

pRBC, packed red blood cells

UES, upper esophageal sphincter

1. INTRODUCTION

Gastroesophageal reflux disease (GERD) can be summarized as mucosal irritation, inflammation and consequential symptoms caused by the reflux of gastric contents into the esophagus due to the impaired function of the gastroesophageal junction (GEJ). It may be accompanied by a wide range of symptoms. Most often, the main symptom is heartburn, a retrosternal pain which may be caused by the regurgitation of gastric acid into the esophagus. In certain cases, it may also be accompanied by dysphagia. Extraesophageal symptoms may often be misleading: in case of proximal (high) reflux, airway symptoms may often be expected; hoarseness, cough, asthma-like episodes, sinusitis or otitis media may also occur. A chest pain of non-cardiac origin or dental caries may also raise the possibility of GERD.

1.1. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

The incidence of GERD shows a significant increase in developed Western countries. Approximately 25 to 40 percent of the US population have reflux symptoms once a month.[1, 2, 3] The incidence of the condition is not lower in Western European countries either; however, the incidence decreases towards the East (primarily in Asia).[4] The increase in the incidence characteristic to the Western world may be, in part, a relative increase, which can be explained by the advance of gastroenterology and the widespread use of esophagogastroscopy. However, due to the transition towards a welfare society, an absolute increase in the incidence must also be taken into account, which can be explained easily with the pathomechanism of the disease: the factors behind the development of GERD include changed dietary habits, the appearance of overweight, increased abdominal pressure due to the previous factors, the altered diet, and the humoral and reflectory effects of medications (that have become part of everyday life) on the reduction of the lower esophageal sphincter tone, as well as the anatomical defects (hiatal hernia) developed because of these. These increase the reflux that is already physiologically present by overcoming the barrier function of the cardiac region. In some cases, depending on the severity of the reflux, the acidic gastric contents regurgitating into the esophagus may cause symptoms only, whereas in other cases, they may damage the squamous epithelium lining the esophagus, resulting in erosion, inflammation and, eventually, ulceration and stricture.[5] The traditional classification of

reflux disease (the Los Angeles Classification)[6] was based on the endoscopic picture, differentiating between cases without signs of inflammation (non-erosive reflux disease, NERD) and those with erosive esophagitis (ERD) or with complications of severe erosion. The Montreal Classification[7], besides the esophageal symptoms, also takes the extraesophageal symptoms, i.e., the complaints of the patients, into account.

In parallel with the severity and duration of GERD, the risk of possible complications also increases. Ulcers and/or strictures developed on the basis of inflammation may lead to severe dysphagia. The condition of acute abdomen/acute chest due to the perforation of an ulcer or stricture may require an urgent (surgical) intervention. Additional possible complications are Barrett's esophagus (BE) and, ultimately, adenocarcinoma developed based on this in the lower third of the esophagus.

1.2. BARRETT'S ESOPHAGUS (BE)

The definition of BE can be understood based on its pathogenesis. As "regeneration" of the mucosal inflammation and, later, mucosal damage developed due to the persistent acid and/or mixed reflux, a columnar epithelium that is more resistant to the acidic environment appears next to or replaces the squamous epithelium in the lower third of the esophagus. The polymorphism of Barrett's metaplasia is reflected by the fact that the regeneration starting from the esophageal Schaffer glands may have varying histological appearance, possibly with multiple histological entities next to each other. Besides intestinal metaplasia (which is considered to be the classic form of BE), numerous other forms may appear, including fundic or cardiac columnar epithelium, ciliary columnar epithelium, or even pancreatic acinar or tubular metaplasia.[8] Although the literature describes the possibility of dysplastic transformation in the case of intestinal metaplasia, non-intestinal forms should not be disregarded either because of the heterogeneity of the condition (histological forms present next to each other or that may transform into each other).

The endoscopic appearance of the metaplasia can be described most accurately with the "Prague C and M" classification[9], which also gives the extension and distance of the lesion from the gastroesophageal junction. An extensive BE longer than 3 cm is a so-called long-segment BE (LSBE), whereas a condition shorter than this is a short-segment BE (SSBE).

1.2.1. Epidemiology of Barrett's esophagus

As to its epidemiology, BE is twice as common in men as in women. A long-term GERD is an independent predictive factor of the condition, and its occurrence increases with age: an age over 50 years can also be considered an independent predictive factor, as well as the Caucasian race. [10] Although smoking seems to be a risk factor in smaller subpopulations, no general conclusion can be drawn from this. According to Swedish studies, both alcohol and smoking should be considered independent risk factors.[11] Obesity and a high BMI also increase the risk of GERD (rather than that of BE), and thus have only an indirect effect on the occurrence of BE.[12] Besides the acidic component in the refluxate, bile acids have a significant pathogenic role in the development of BE.[13,14]

The incidence of BE is hard to estimate. With endoscopy becoming a daily routine, it seems to be more and more common[11]. However, it is important to emphasize that the differences in its definition due to the histological polymorphism of the condition also have an effect on the numerical epidemiological data.[11] In the West–East comparison, the incidence of BE decreases towards the East.[11] The prevalence of BE in the North American and Western European population is an estimated 0.9 to 10 percent.[11,15,16,17,18] Based on the data of the Surveillance Epidemiology and End Results (SEER) cancer registry, the estimated prevalence of BE is 5.6% in the normal population[19]. Swedish data calculate with a prevalence of about 1.6%. In the case of GERD, it may be up to 2.3%. In two-thirds (64%) of the BE cases, SSBE is observed. According to a North American study, the prevalence of LSBE among patients examined with endoscopy is 0.3 to 2%, and this figure is naturally higher (8 to 20%) if the indication for endoscopy was symptomatic GERD. It should be noted that there is asymptomatic persistence in the majority of LSBE cases and often, the condition is not even recognized. The prevalence of SSBE is higher, between 5 and 30 percent, and there is a 7 to 8 times higher occurrence of cardiac and specialized intestinal metaplasia than in the case of LSBE, although dysplasia is considerably less common in SSBE.[11]

Based on cancer registries, esophageal cancer is the eighth most common malignant disease. The incidence of esophageal squamous cell cancer in the developed Western world has been stagnating or slightly decreasing since the 1970s and 1980s.[20] Contrary to this, the incidence of adenocarcinoma is gradually increasing.[13]

Although BE has an important role as the only known and confirmed precancerous condition in the development of lower-third esophageal adenocarcinoma, it cannot be considered an obligatory condition of it, since, in many cases, BE is not found during the histological

examination. Based on large clinical studies, it can be established that the incidence of adenocarcinoma in case of BE is 6.1/1000 patient years.[21] The risk in men is twice as high as in women.[13,21] As to the process of carcinogenesis, it is supposed that adenocarcinoma is developed through the metaplasia–low-grade dysplasia–high-grade dysplasia transition. In case of low-grade dysplasia (LGD) developed on the basis of intestinal metaplasia, the risk of malignant transformation is increased.[22] According to Stein, the presence of in situ carcinoma is almost certain in the case of high-grade dysplasia (HGD). [23] To summarize, the increase in the occurrence of GERD consequentially increases that of BE, which may explain the increasing trend in the occurrence of esophageal adenocarcinoma (contrary to what is observed in the case of squamous cell cancer) in the developed world.[20,22]

1.3. DIAGNOSTICS OF GERD AND BE

Besides the proper evaluation of the patient's symptoms, many instrumental examination methods are available to clarify the diagnosis. Flexible endoscopy, with its advance and widespread use, has clearly become the gold standard in the assessment of the esophagus. Without a proper endoscopic background, a thorough investigation of neither GERD, nor BE can be performed. The new endoscopic examination methods (such as chromoendoscopy, NBI, etc.) may help map GERD and BE more precisely. The need for proper professional experience and technical equipment warrants the investigations to be performed in centers.

The objective confirmation and description of reflux and, ultimately, making the indication for surgery are also inconceivable without proper functional examinations. The gastroenterologist may decide about the correct treatment strategy in the knowledge of the presence of acid or bile reflux obtained with pH-metry, impedance monitoring and Bilitec monitoring.[24] The information about the function, motility disorders and impairment of the esophageal body and sphincters gained during manometry may influence the choice of surgical procedure. [25] A proper biopsy sampling procedure (Seattle protocol) [26] and a well-prepared pathological background are also indispensable for detecting the presence of BE.

1.4. TREATMENT OF GERD AND BARRETT'S ESOPHAGUS

The conservative (non-surgical) treatment is extremely complex and involves losing weight (besides other lifestyle advices), increasing stomach emptying (with prokinetics), protecting the esophageal mucosa, and decreasing the acid content of the refluxate.

Nowadays, the medical treatment is primarily based on effective gastric acid-reducing therapies. The symptoms of reflux can be considerably improved with proton-pump inhibitor therapy, the use of which may mean an adequate long-term control of reflux. Similarly, they can be effective in the treatment of some patients with BE (but there is only indirect evidence of their efficacy in the treatment of metaplasia and dysplasia).[27] In case of BE, aspirin in increased dose may be added to antacids as chemoprevention, which may reduce the risk of transition from metaplasia to dysplasia through the inhibition of COX-2.

The purpose of the endoscopic treatment of BE is to remove or destroy the affected mucosa when dysplasia appears, after which the regeneration restores the squamous epithelium or results in a dysplasia-free columnar epithelium if the treatment is combined with successful acid inhibitor therapy. Numerous procedures are known from endoscopic mucosal resection to submucosal dissection. Ablation may be achieved with radiofrequency therapy but laser therapy, argon plasma coagulation, cryotherapy and photodynamic therapy may also be used. Out of these methods, however, the depth of the dissection can be reconstructed and an actual histological examination can be performed only in the case of endoscopic resections. In the rest of the procedures, there is less control of the ablation depth, and the rate of potential complications (stricture and, more rarely, perforation) is higher. The indication for endoscopic procedures is not clear in case of LGD. A special issue is recurrence in the submucosal glandular structures after the endoscopic treatment. In case of LGD, the rate of this may be up to 10% in the year following the procedure. However, an advantage of the endoscopic procedure is that it can be repeated. [28]

In case of HGD, the higher relapse rate after endoscopic procedures or the appearance of carcinoma may require surgical intervention. The presence of in situ carcinoma is almost certain in the case of HGD; however, neither this, nor an early carcinoma means a contraindication to endoscopic procedures. [28]

1.4.1 Surgical Treatment

The various antireflux procedures have long been accepted in the surgical treatment of GERD and BE. Nowadays, with the spread of minimally invasive surgical methods, laparoscopic antireflux procedures that have low mortality rates have become equivalent alternatives to conservative treatment. In case of proper indication, the correctly performed procedure successfully decreases the acid and bile reflux, and also restores the function of the lower esophageal sphincter. In case of BE, with the reflux gone, we may suppose that the progression of metaplastic and dysplastic processes is stopped and that regression is achieved. The long-term success of antireflux procedures, similarly to that of medical treatment, is contradictory, as well as their role in the prevention of adenocarcinoma. In cases of BE with LGD, better results may be expected from the combination of mucosal ablation and medical or surgical treatment. In cases of HGD, in situ carcinoma and early cancer, distal esophageal and cardiac resection may be considered an oncologically adequate treatment from a surgical point of view. In case of invasive adenocarcinoma, esophageal resection may be performed.

2. PROBLEMS AND OBJECTIVES

The increase in the incidence of esophageal adenocarcinoma calls the importance of this condition to our attention. The key for the successful treatment of esophageal adenocarcinoma is the prevention of its development or its early recognition. The only precancerous condition of esophageal adenocarcinoma confirmed to date is BE. In our clinical study, we intended to establish the clinical risk factors of the development of BE, the prevention of its development, and the possible strategy for its surgical treatment.

1. An objective of our work was to understand the potential clinical risk factors and relationships playing a role in the development of BE and the process of the Barrett's metaplasia—dysplasia—carcinoma transformation through the study of patients with GERD and BE (Study 1).

2. A further objective was to study the efficacy of surgical treatment (laparoscopic antireflux procedure) among patients subjected to surgery because of either GERD or BE (Study 2).

3. During our short-term and long-term follow-up, the effect of laparoscopic antireflux procedure on the histological changes of Barrett's esophagus, as well as its possible preventive effect in the process of carcinogenesis were studied (Study 3).

4. The early and late complications of the antireflux procedure were studied (Study 4).

5. The successful endoscopic treatment of spontaneous esophageal perforation, a rare complication of BE, is presented through one of our cases (Study 5).

3. PATIENTS AND METHODS

3.1. COMPARISON OF PATIENTS SUBJECTED TO SURGERY BECAUSE OF GERD OR BE (STUDY 1)

Our retrospective clinical study was based on patients subjected to surgery because of GERD or reflux disease accompanied by Barrett's esophagus at the Department of Surgery of the Faculty of Medicine of the University of Szeged between January 1, 2001 and December 31, 2008. Nissen's laparoscopic antireflux procedure was performed in 176 cases because of GERD (Group 1) and in 78 cases because of BE (Group 2).
In Study 1, the results of the preoperative assessment were compared between the above two patient groups.

3.2. CLINICAL RISK FACTORS OF THE DEVELOPMENT OF BE

As a continuation of Study 1, patients in the BE group (78 patients) were divided into three further groups on the basis of the histological results of their preoperative endoscopic biopsies: a non-intestinal group (NI, 53 patients) with fundic (FM) and cardiac metaplasia (CM), an intestinal group (I, 18 patients) with intestinal metaplasia (IM), and a dysplastic group (D, 7 patients) with LGD. BE involved a short segment (< 3 cm, SSBE) in 67 cases (85.9%) and a long segment (> 3 cm, LSBE) in 11 patients (14.1%). We compared the results of the preoperative assessment between these three groups.

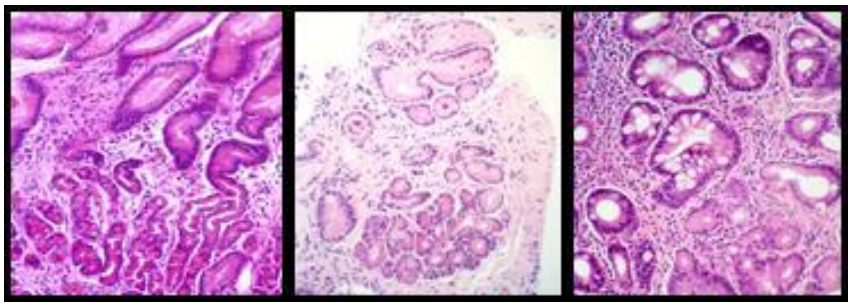
3.3. COMPONENTS OF THE PREOPERATIVE ASSESSMENT

3.3.1. Endoscopy

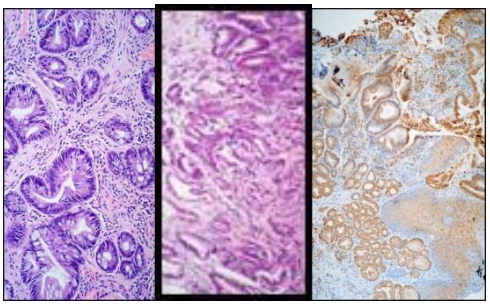
The esophagogastroscopy performed as part of the preoperative gastroenterological assessment to confirm the reflux disease was the first step of the standard examination, during which the gastroesophageal junction was examined. Hiatal hernia is diagnosed if the impression of the diaphragmatic crura is widened by more than 2 cm. Its size is given in centimeters. The reflux disease was described based on the Los Angeles Classification. [6] Biopsy was performed (in all four quadrants, with 2-cm intervals) to confirm or rule out Barrett's metaplasia (Seattle protocol). [26] Barrett's esophagus was characterized based on the Prague C & M Criteria. [9]

3.3.2. Histological Examination

The formalin-fixed, paraffin-embedded histological samples were assessed for Barrett's metaplasia or dysplasia after hematoxylin-eosin and immunohistochemistry staining (Figure 1). In our study, samples with either fundic or cardiac or intestinal metaplasia were included. In case of BE with LGD described during the histological examination, two experienced pathologists also examined the slides.



FM, CM, IM



LGD, HGD, COX-2 activity

Figure 1. Histological examination of BE.
Hematoxylin-eosin staining and immunohistochemistry.

3.3.3. Functional Examinations

Esophageal pH-metry

Of the functional examinations, 24-hour pH-metry was performed in each case. The acid reflux was measured with a pH electrode inserted nasally and secured 5 cm above the upper margin of the lower esophageal sphincter (LES). The probe recorded the acid reflux episodes for 24 hours—esophageal pH decrease below 4, number of reflux episodes longer than 5 minutes, duration of the longest reflux episode, percentage of time of exposure to pH below 4, and the DeMeester composite score, out of which the DeMeester score and the percentage of time of exposure to pH below 4 have the highest sensitivity (96%) and specificity (100%). Their normal value, based on studies conducted with health volunteers, is 14.7 and 4.2%, respectively.[29,30,31,32,33]

Esophageal manometry

During the manometry, the motor function of the esophagus was examined with a catheter inserted nasally into the esophagus, using the standard distilled water perfusion method, and mapping the function of the entire esophageal body, the pharyngoesophageal junction and the LES: the length of the sphincter (lLES), its mean pressure (pLES), its relaxation (rLES), the amplitude and duration of the contractions of the esophageal body, and (optionally) pharyngeal motility. The generally accepted values for the UES are a length of 2 to 5 cm and a mean pressure of 40 to 100 mmHg; and for the LES, a length of 2 to 4 cm and a mean pressure of 10 to 40 mmHg. The pressure in the lower third of the esophagus during swallowing is 20 to 170 mmHg.[29,34,35,36]

Bilitec

In both groups, Bilitec monitoring was performed only in cases where bile regurgitation was suspected during endoscopy. The nasally inserted catheter was positioned 5 cm above the LES, and the photoabsorption (at 450 nm) of bile acids reaching the esophagus was detected with a fiber optic spectrophotometer.[29, 30,31,32]

3.4. SURGICAL TREATMENT, SURGICAL TECHNIQUE

After the gastroenterological assessment, patients with GERD and BE underwent elective surgery. Laparoscopic antireflux procedure with Nissen's 360-degree fundoplication was performed on the patients of both groups. During the standardized steps of the procedure, the flaccid part of the lesser omentum was opened while retracting the left lobe of the liver, and then the diaphragmatic crura were prepared (first the right, and then the left one), going around the entire circumference of the esophagus, mobilizing this way its abdominal segment. The fundus was mobilized by transecting the gastrosplenic ligament and the short arteries and veins running within it. The posterior reconstruction of the diaphragmatic crura was performed with interrupted stitches (using non-absorbable suture). After this, 360-degree (Nissen's) fundoplication was performed in each case. Partial (Toupet) and anterior (Dor) fundoplications were excluded from the study.

During the surgeries, a mesh was placed because of the large hiatal hernia in 14 cases. The indication for this was the unsuccessful tension-free closure of the diaphragmatic crura. A PTFE mesh was used for the reconstruction, which was secured with a spiral clamp. Gastropexy was performed in 6 cases in the GERD group, and a mesh was also placed in each of these cases because of a large hiatal hernia. In 26 cases, cholecystectomy was also performed in the same session because of the accompanying cholelithiasis.

3.5. POSTOPERATIVE FOLLOW-UP (STUDY 2)

During Study 2, the efficacy of procedures performed because of GERD or BE were compared based on subjective measures (Visick score) and the results of early functional examinations.

Assessment of symptoms and objective measures of outcome

Visick grading was used to assess the effect of surgery on the symptoms: complete resolution (Grade I); an improvement (Grade II); no effect of surgery (Grade III); or deterioration relative to the preoperative state (Grade IV). This scoring system was devised to give an overall impression of the benefits of antireflux surgery because it exhibits good correlation with heartburn, the most prominent symptom of GERD.[37]

In the postoperative period, patients were subjected to follow-up surgical and medical examinations. Postoperative functional examinations, such as esophageal manometry, 24-hour pH-metry and, in reasonable cases, bile exposure (Bilitec) monitoring and endoscopy were performed in the early postoperative period with an average follow-up period of 13.8 ± 19.31 months in the GERD group and 16.7 ± 17.00 months (range: 3–23) in the BE group.

3.6. ENDOSCOPIC AND HISTOLOGICAL FOLLOW-UP OF PATIENTS SUBJECTED TO LAPAROSCOPIC ANTIREFLUX PROCEDURE BECAUSE OF BE (STUDY 3)

During the study, in the later postoperative period, an additional upper endoscopy with biopsy was carried out in the BE subgroups to assess the changes in BE. The overall average follow-up time was 42 ± 16.19 months (range: 3–61).

3.7. STUDY OF THE COMPLICATIONS OF THE ANTIREFLUX PROCEDURE (STUDY 4)

The *early* complications of laparoscopic antireflux procedure are well known. *Bleeding* may start from the vessels that supply the stomach (left gastric artery and vein and short gastric arteries and veins). Spleen injury during the mobilization of the fundus may be a severe condition that often requires conversion. Injury to the hepatic capsule and bleeding of the liver are rarely severe complications. Rarely, the iatrogenic or ischemic *perforation* of a hollow organ (esophagus, stomach) may require an intraoperative solution or early reoperation. *Subcutaneous emphysema* due to the insufflation, which involves less risk, rarely requires surgical intervention. *Pneumothorax* accompanying pleural injuries in the posterior mediastinum, however, may require pleural drainage in certain cases. Impaired gastric emptying as a consequence of *injury* to the *vagus* nerve fibers may cause complaints in the long term.

Among the *late* complications of the surgical treatment, persistent cases of *dysphagia* must be mentioned first, the treatment of which, similarly to making the indication for surgery, requires a close cooperation between the gastroenterologist and the surgeon. In case of an

unsuccessful dilation with bougies, balloon dilation may be required. In case of large *hiatal hernias*, the placement of a mesh exposes the patient to special hazards. *Erosion* of the esophageal wall may be a severe or even life-threatening condition, and it is to be treated surgically with relative urgency: often, cardiac resection and jejunal interposition (Merendino's procedure) are required.

3.8. COMPLICATIONS OF BE (STUDY 5)

Stricture, *bleeding*, perforation and, ultimately, *malignant transformation* on the basis of Barrett's ulcer are well-known complications. Perforation as a consequence of Barrett's ulcer or a stricture is most often iatrogenic. Spontaneous perforation is an extremely rare, life-threatening condition. The successful endoscopic treatment of this rare complication will be presented through a case report.

3.9. STATISTICAL ANALYSIS

The values measured and summarized during the clinical study of the GERD and BE groups were evaluated using SigmaStat® 3.1, comparing the groups with a two-sample t test and the Mann–Whitney Rank Sum test. Further statistical calculations were performed with SPSS 17.0 for Windows, whereas the special Poisson-distributed ANOVA method was performed with SAS for Windows 9.1.[38] Preoperative univariate analyses were performed to identify factors associated with the occurrence of histopathological progression: a non-parametric method (Kruskal–Wallis test) was used for the analysis of variables. Non-parametric univariate analyses (Mann–Whitney test) were performed to estimate the efficacy of laparoscopic antireflux surgery, comparing the variables before and after surgery. To compare changes in the patients' parameters before and after the operation in the three BE groups, a generalized mixed model repeated measurements ANOVA method was applied (multivariate analysis), using the GLIMMIX procedure of SAS 9.1. One repeated measurement factor (antireflux surgery), one independent factor (groups) and their interaction were examined. The distribution of the variables and the differences of variations in the three BE groups were also taken into account. P values < 0.05 were considered statistically significant.

4. RESULTS

4.1 COMPARISON OF PATIENTS SUBJECTED TO SURGERY BECAUSE OF GERD OR BE (STUDY 1)

According to the results of Study 1, the gender distribution in the two patient groups showed a predominance of women (112 women, 64 men), with a more balanced ratio in cases complicated with Barrett's esophagus (40 women, 38 men) but, contrary to literature data, there was no male predominance in this group either (Table 1). There was no difference between the two groups in mean patient age (Group 1: 53.87 ± 12.04 years vs. Group 2: 53 ± 12.7 years, p=0.495) or mean BMI (Group 1: 26.91 ± 4.54 vs. Group2: 28.31 ± 5.46, p=0.451). It must be noted, however, that the majority of patients in both groups were overweight, which is a known potential risk factor of reflux disease (Table 1).

	GERD mean and SD	**BE** mean and SD
MEAN AGE (years)	**53.87**±12.04	**53.03**±12.70
GENDER DISTRIBUTION (MEN/WOMEN)	**64/112**	**38/40**
BMI	**26.91**±4.54	**28.31**±5.46
HISTORY (MONTHS)	**68.86**±32.63	**68.98**±60.89
DURATION OF MEDICAL THERAPY (MONTHS)	**19.87**±25.17	**19.20**±27.31
RATE OF HIATAL HERNIA (%)	**75.56**	**64.10**
SIZE OF HIATAL HERNIA (CM)	**3.50**±1.59	**3.73**±1.71

Table 1. Demographics and historical data of patients with GERD and BE
There was no statistical difference in the demographics between GERD and BE patients.

As to the results of the preoperative assessment, contrary to our hypothesis, there was no difference between the two groups in the mean time from the onset of symptoms to the surgery (p=0.653). A relatively long history was observed in both patient groups (68.86 ± 32.63 months in Group 1 and 68.98 ± 60.89 months in Group 2) (Table 1). In both groups, the

complaints of the patients mostly included heartburn, epigastric or chest pain, acid or bile belching, dysphagia, loss of appetite, nausea, and vomiting.

In all of the cases, surgery was performed after an unsuccessful acid-reducing medical therapy (mean duration of treatment: 19.87 ± 25.17 months in Group 1 and 19.20 ± 27.31 months in Group 2). As expected, hiatal hernia was common among the patients (in 75.42% in Group 1 [133 cases] and in 64.10% in Group 2 [50 cases]). Its mean size, however, was almost the same in the two groups (3.48 ± 1.59 vs. 3.73 ± 1.71 cm [p=0.296]) (Table 1). A mesh was placed because of a large hiatal hernia in 10 cases (5.7%) in Group 1 and in 4 cases (5.1%) in Group 2.

The theory according to which bacterial colonization, and metabolites produced during bacterial metabolism, are potentially carcinogenic, was not supported in the case of BE by the Helicobacter pylori infection observed in the stomach (confirmed in 27% in Group 1 and in only 22% in Group 2). Besides the reflux, the accompanying gastritis was also often observed during the endoscopic examination.

4.1.1. Preoperative Functional Results

Manometry

Although it can be established that the LES function measured with manometry was impaired in both groups, thus allowing abnormal acid and/or bile reflux, there was no difference between the two groups in the mean values of LES pressure (12.10 ± 7.93 mmHg vs. 12.57 ± 9.03 mmHg [p=0.892]), relaxation time (10.39 ± 2.99 sec vs. 10.36 ± 2.81 sec [p=0.773]) and length (3.30 ± 1.84 cm vs. 3.17 ± 1.45 cm [p=0.377]) (Table 2).

pH-metry

Based on the results of pH-metry—in accordance with the pathomechanism of the disease—the acid reflux was more severe in patients subjected to surgery because of Barrett's esophagus than in those with reflux disease alone. During the pH-metry performed 5 cm above the cardia, the total number of reflux episodes (measured over 24 hours), the number of upright episodes, the number of supine episodes, the number of postprandial episodes, the number of episodes longer than 5 minutes, and the value of the longest episode were all significantly higher in Group 2 ($p<0.001$). The DeMeester score was also higher in Group 2 (18.9 vs. 41.9, $p<0.001$) (Table 2).

PREOPERATIVE FUNCTIONAL RESULTS	GERD	BE	p value
LES	**mean±SD**	**mean±SD**	
PRESSURE (mmHg)	**12.10±**7.93	**12.58±**9.03	NS
RELAXATION TIME (sec)	**10.39±**2.99	**10.37±**2.81	NS
LENGTH (cm)	**3.02±**1.84	**3.17±**1.45	NS
pH-METRY			
Total time of acid exposure <pH 4	**65.62±**69.39	**123.11±**134.71	<0.001
Upright acid exposure <pH 4	**55.37±**58.21	**97.84±**112.53	<0.001
Supine acid exposure <pH 4	**11.00±**23.21	**25.49±**36.68	<0.001
Postprandial acid exposure <pH 4	**31.34±**34.42	**55.55±**57.77	<0.001
>5 min acid exposure <pH 4	**2.20±**3.64	**4.55±**6.72	<0.001
Longest acid exposure <pH 4	**12.04±**17.50	**25.96±**49.80	<0.001
DeMeester score	**18.85±**21.39	**41.93±**51.15	<0.001
Bilitec			
Total time of bile exposure	**10.50±**17.72	**26.97±**28.79	<0.001
Upright bile exposure	**10.33±**17.79	**17.41±**19.70	NS
Supine bile exposure	**0.17±**0.39	**9.80±**15.17	NS
Postprandial bile exposure	**5.58±**10.01	**8.30±**9.84	NS
>5 min bile exposure	**2.00±**4.24	**6.69±**9.53	<0.001
Longest bile exposure	**16.17±**20.44	**82.96±**105.14	<0.001

Table 2. Results of preoperative functional examinations in patients with GERD and BE
Based on the preoperative functional examinations, the impairment of the function (pressure) of the LES was the same in both patient groups. Patients with BE were characterized by more severe and more frequent acid reflux episodes.

Bilitec

Bilitec monitoring was performed only in a limited number of GERD cases, primarily if bile reflux was suspected during endoscopy. Because of the selected cases, a statistical conclusion cannot be drawn; however, in view of the Bilitec results, it can be established that the values of the total time of bile reflux and the number of bile reflux episodes longer than 5 minutes were higher, and the longest bile reflux episode was longer in the case of patients subjected to surgery because of Barrett's esophagus (Table 2).

4.1.2. Comparison of the functional examinations of patients subjected to surgery because of BE based on the histological severity of BE

Preoperative characteristics of the BE patient population (NI, I and D groups)

Contrary to our expectations, IM and LGD did not show a longer history of reflux disease when compared with the NI group, and history was longer in the NI group than in the I group (p=0.057) (Table 1). The duration of medical treatment showed no difference either. Although patients were overweight in all 3 groups, there was no difference in mean BMI. Hiatal hernia was present with the same incidence in cases of more severe BM and LGD, but it was not significantly higher than in the NI group. No statistical difference was detected between the 3 groups in the LES function (pressure, length and relaxation time). In accordance with literature data, our research results revealed more severe acid reflux in patients with BE than in patients with mild GERD alone. With respect to acid reflux, however, BE did not exhibit any difference. The parameters used to calculate the DeMeester score did not differ significantly between the 3 groups. In comparison with the NI group, a higher DeMeester score was observed only in the D group, but this difference was not significant. The majority of the values measured during the Bilitec monitoring indicated more severe bile reflux in the D group than in the other 2 groups (Table 3). In contrast with the results of the univariate analyses, the multivariate analysis did not demonstrate significant differences between the three preoperative groups.

		Group	Mean	SD	p value
Patients' characteristics	**BMI**	NI	27.70	5.58	
		I	29.93	5.67	p=0.354
		D	28.30	4.09	
	Hiatal hernia (cm)	NI	3.07	1.95	
		I	3.08	2.4	p=0.395
		D	4.20	1.17	
	Mean time (years) from appearance of first symptoms to surgery	NI	5.80	4.53	
		I	3.94	5.25	p=0.057
		D	4.29	5.15	
	PPI treatment (y)	NI	1.47	2.56	
		I	1.00	0.97	p=0.537
		D	4.14	5.27	
Manometry	**pLES (mmHg)**	NI	11.27	8.19	
		I	13.31	8.84	p=0.382
		D	8.40	8.85	
	rLES (s)	NI	10.51	3.32	
		I	10.09	1.97	p=0.937
		D	10.00	0.82	
	lLES (cm)	NI	2.98	1.37	
		I	3.54	1.90	p=0.757
		D	3.00	0.82	
pH-metry	**Total time of acid exposure <pH 4**	NI	100.64	78.11	
		I	111.12	104.80	p=0.835
		D	274.20	359.82	
	Upright acid exposure <pH 4	NI	80.10	70.91	
		I	93.18	92.16	p=0.832
		D	229.00	302.06	
	Supine acid exposure <pH 4	NI	20.67	25.10	
		I	18.35	29.21	p=0.374
		D	45.60	60.65	
	Postprandial acid exposure <pH 4	NI	47.28	38.05	
		I	50.88	55.35	p=0.748
		D	113.20	136.51	
	>5 min acid exposure <pH 4	NI	3.90	4.76	
		I	5.06	10.05	p=0.299
		D	8.00	8.80	
	Longest acid exposure <pH 4	NI	25.10	60.13	
		I	15.24	20.97	p=0.469
		D	43.20	48.98	
	DeMeester score	NI	34.95	43.84	
		I	39.12	61.01	p=0.145
		D	88.92	67.58	
Bilitec	**Total time of bile exposure**	NI	22.38	22.90	
		I	23.33	30.53	p=0.025
		D*	70.75	32.52	
	Upright bile exposure	NI	13.88	17.64	
		I	16.60	15.77	p=0.027
		D*	48.75	28.36	
	Supine bile exposure	NI	8.66	12.16	
		I	6.80	19.04	p=0.017
		D*	23.00	14.90	
	Postprandial bile exposure	NI	6.78	9.30	
		I	8.00	7.85	p=0.087
		D	20.50	16.84	
	>5 min bile exposure	NI	6.97	10.27	
		I	3.00	2.90	p=0.021
		D*	17.50	14.39	
	Longest bile exposure	NI	87.16	107.20	
		I	38.60	63.72	p=0.195
		D	111.25	37.95	

Table 3. Characteristics of the three preoperative groups (NI, I and D) (78 patients)
*Comparison of the preoperative BE groups revealed significantly more severe bile reflux in the D group than in the other two groups. (Non-parametric method—the Kruskal–Wallis test was applied)

4.2. POSTOPERATIVE RESULTS (STUDY 2)

In part 2 of the study, the efficacy of the antireflux surgery was assessed in view of the postoperative results.

4.2.1. Symptomatic Outcome

Based on the Visick score[17] determined in Group 1 after the surgery, at the early surgical follow-up visit (at 3 months), complaints were gone or improved in 73% of the patients, they were unchanged in 15%, and 12% of the patients reported worsening, primarily with a leading symptom of dysphagia. In Group 2, 81% of the patients were complaint-free or reported improved symptoms, 15% had unchanged complaints, and worsening was observed in 4%. Dysphagia was the predominant symptom also in this group.

4.2.2. Postoperative Functional Results

After the surgery, patients were subjected to follow-up functional examinations and endoscopy; the mean follow-up time was 13.8 ± 19.31 months in Group 1 and 16.7 ± 17.00 months in Group 2. The mean LES pressure was significantly increased compared with the preoperative value in both groups (17.58 ± 7.60 mmHg in Group 1 and 18.70 ± 6.74 mmHg in Group 2). After the surgery, the LES length and relaxation time did not show a statistically significant difference compared with the preoperative values (Table 4).

Based on the follow-up pH-metry, the number and duration of acid reflux episodes significantly decreased in both groups. The postoperative DeMeester scores returned to the normal range: they decreased to a mean score of 7.7 ± 17.41 in Group 1 and 12.7 ± 30.74 in Group 2. When following the patients subjected to Bilitec monitoring before the surgery, a decrease in the occurrence of bile reflux was also observed (Table 4).

FUNCTIONAL RESULTS	GERD			BE		
	Preop	**Postop**	**p value**	**Preop**	**Postop**	**p value**
LES	mean ± SD	mean ± SD		mean ± SD	mean ± SD	
PRESSURE (mmHg)	12.10±7.93	17.58±7.60	<0.001	12.58±9.03	18.70±6.74	<0.001
RELAXATION TIME (s)	10.39±2.99	9.31±2.60	NS	10.37±2.81	10.25±2.22	NS
LENGTH (cm)	3.02±1.84	3.39±1.34	NS	3.17±1.45	3.48±1.85	NS
pH-METRY						
Total time of acid exposure <pH 4	65.62±69.39	18.04±37.96	<0.001	123.11±134.71	47.08±89.16	<0.001
Upright acid exposure <pH 4	55.37±58.21	14.33±33.43	<0.001	97.84±112.53	37.18±71.51	<0.001
Supine acid exposure <pH 4	11.00±23.21	3.53±8.77	<0.001	25.49±36.68	9.96±22.63	<0.001
Postprandial acid exposure <pH 4	31.34±34.42	8.38±21.15	<0.001	55.55±57.77	22.02±43.14	<0.001
>5 min acid exposure <pH 4	2.20±3.64	0.56±2.14	<0.001	4.55±6.72	0.80±2.20	<0.001
Longest acid exposure <pH 4	12.04±17.50	6.24±20.75	<0.001	25.96±49.80	3.58±5.82	<0.001
DeMeester score	18.85±21.39	7.73±17.41	<0.001	41.93±51.15	12.72±30.74	<0.001
Bilitec						
Total time of bile exposure	10.50±17.72	17.00±22.24	NS	26.97±28.79	22.08±30.57	<0.001
Upright bile exposure	10.33±17.79	15.25±19.38	NS	17.41±19.70	18.24±26.14	NS
Supine bile exposure	0.17±0.39	2.00±3.37	NS	9.80±15.17	3.92±7.78	NS
Postprandial bile exposure	5.58±10.01	9.00±13.47	NS	8.30±9.84	7.52±11.16	NS
>5 min bile exposure	2.00±4.24	2.50±3.00	NS	6.69±9.53	3.00±4.61	<0.001
Longest bile exposure	16.17±20.44	53.50±46.94	NS	82.96±105.14	58.88±131.77	<0.001

Table 4. Results of postoperative functional examinations in patients with GERD and BE
The postoperative functional examinations confirmed an increase in LES pressure and a decrease in bile reflux in both groups.

4.2.3. Postoperative Results by BE Subgroup (Study 3)

In part 3 of the study, the rate of BE regression was studied in function of the laparoscopic antireflux surgery. The early quality of life measures, the results of the early postoperative functional examinations and the long-term endoscopic follow-up results were summarized for the three BE subgroups.

4.2.3.1. Early postoperative results

4.2.3.1.1. Symptomatic outcome

The Visick score varied somewhat within the groups—in patients with intestinal BE and also in those with LGD, complaints were alleviated relative to those with NI metaplasia. The assessment of the changes in both the subjective and objective complaints demonstrated that the symptoms recorded during the preoperative period tended to be relieved after laparoscopic Nissen fundoplication. In accordance with our expectations, dysphagia increased.

4.2.3.1.2. Postoperative functional examinations (manomentry, 24-hour pH studies and Bilitec)

Postoperative manometry, pH-metry and Bilitec monitoring did not reveal statistically significant differences between the three groups. Changes in the LES function, which also indicate the efficacy of the surgery, demonstrated that the postoperative pressure in the lower esophagus was significantly increased relative to that measured preoperatively, whereas the relaxation time remained unchanged. As a consequence of the surgical technique (a loose and narrow Nissen floppy), the length of the LES was unchanged after fundoplication, but its function (pressure) was restored, thus preventing acid and bile reflux. Comparison of the results of pH-metry before and after the procedure between the three groups confirmed the above findings, as mean DeMeester scores were clearly decreased after the surgery. Accordingly, the incidence and severity of bile reflux were reduced, or this symptom was eliminated. The multivariate analysis confirmed significant changes only in LES pressure and the results of pH-metry between the preoperative and postoperative groups.

4.3 RESULTS OF THE ENDOSCOPIC FOLLOW-UP OF THE BE SUBGROUPS (ENDOSCOPIC SURVEILLANCE) - Long-term endoscopic surveillance

The mean duration of endoscopic follow-up was 42 ± 16.19 months. Postoperative endoscopy was performed only in 64 patients (82%, 64/78). 14 patients, who were not subjected to upper gastrointestinal endoscopy, were excluded from the long-term analysis.

Before the antireflux surgery, SSBE was present in 56 patients and LSBE in 8 patients. Preoperative histological examinations indicated FM in 11, CM in 33, IM in 15 and LGD in 5 patients. The postoperative check-up demonstrated a total regression of BE in 10 patients (15.6%). Partial regression was seen in 9 cases (14.1%), no further progression in 34 patients (53.1%), and progression from FM to CM in 4 patients (6.2%) or from CM to IM in 7 patients (11%), but no cases of dysplastic or malignant transformation were recorded. There was no further progression in the patients with LGD, and in 3 of these 5 patients, LGD disappeared, leaving only residual IM (Table 5).

	Complete regression	Partial regression	No change	Progression
Overall group				
SSBE (n=56)	10 (17.9%)	5 (8.9%)	30 (53.6%)	11 (19.6%)**
LSBE (n=8)	0	4 (50%)	4 (50%)	0
NI* (n=44)	6 (13.6%)	4 (9.1%)	23 (52.3%)	11 (25%)**
IM (n=15)	3 (20%)	3 (20%)	9 (60%)	0
LGD (n=5)	1 (20%)	2 (40%)	2 (40%)	0
Total (n=64)	**10 (15.6%)**	**9 (14.1%)**	**34 (53.1%)**	**11 (17.2%)****

Table 5. Endoscopic and histopathological changes of BE after laparoscopic fundoplication (64 patients)

Complete regression of BE was defined as the absence of any visible metaplasia on endoscopy and the absence of columnar metaplasia on histopathological examination. Partial regression was defined as a regression from LSBE to SSBE, or a regression from dysplasia to metaplasia, or changes within the metaplastic group (IM>CM>FM). Aggravation of the disease was defined as changes within the metaplastic group (FM<CM<IM), or progression from metaplasia to dysplasia or from SSBE to LSBE. Results are expressed as numbers of patients with percentages in parentheses.

* NI, including fundic and cardiac metaplasias

** progression from FM to CM in 4 patients and from CM to IM in 7 patients; no further progression in patients with IM or LGD

There was no difference in the length of the follow-up period between the total regression group and the other groups (partial, no change and progression). Where the regression of BE was observed, the postoperative functional examination results of manometry (pLES) and pH-metry were significantly better compared with those measured in the groups where no changes in BE occurred, or progression of BE was found. We did not find differences between the groups in the results of postoperative Bilitec monitoring, except for the longest exposure values (Table 6).

		Groups			
		Regression (SD)	**No change (SD)**	**Progression (SD)**	**p value**
Manometry	pLES (mmHg)	18.04 (±6.405)	9 (±7.735)	11.02 (±7.815)	0.003
	rLES (s)	10.04 (±1.613)	10.03 (±2.831)	9.89 (±4.285)	0.988
	lLES (cm)	3.21 (±0.699	3.14 (±1.424)	2.89 (±1.269)	0.571
pH-metry	Total time of acid exposure <pH 4	23.77 (±25.21)	105.29 (±89.191)	112.2 (±82.974)	<0.001
	Upright acid exposure <pH 4	21.23 (±24.1229	79.79 (±67.776	87.9 (±74.929)	0.002
	Supine acid exposure <pH 4	2.62 (±3.595	25.75 (±33.216)	24.6 (±21.798)	0.002
	Postprandial acid exposure <pH 4	12.42 (±16.649)	48.63 (±46.04)	61.3 (±53.506)	0.009
	>5 min acid exposure <pH 4	0 (±0)	5.46 (±8.495)	5.1 (±5.607)	<0.001
	Longest acid exposure <pH 4	1.38 (±1.557)	19.33 (±27.223)	19.6 (±15.82)	<0.001
	DeMeester score	3.52 (±3.617)	40.88 (±51.37)	43.089 (±6.094)	<0.001
Bilitec	Total time of bile exposure	4.75 (±6.292)	32.05 (±34.861)	23 (±28.605)	0.097
	Upright bile exposure	4 (±4.83)	19.21 (±22.062)	15.89 (±18.395)	0.143
	Supine bile exposure	0.75 (±1.5)	13.05 (±19.478)	7.44 (±12.69)	0.295
	Postprandial bile exposure	1 (±1.414)	8.11 (±10.954)	7.89 (±10.55)	0.117
	>5 min bile exposure	0.75 (±1.5)	9.05 (±13.206)	6.33 (±9.206)	0.138
	Longest bile exposure	3.25 (±5.188)	81.72 (±99.8)	72.78 (±93.641)	0.050

Table 6. Comparison of the postoperative functional examinations and the changes in BE (between the three groups: regression, no change, progression (64 patients).

4.4. COMPLICATIONS OF MINIMALLY INVASIVE ANTIREFLUX PROCEDURES AND THEIR TREATMENT (STUDY 4)

4.4.1. Surgical complications

In part 4 of our study, the risk of the surgical treatment was evaluated. We processed the data on surgical complications of patients subjected to surgery because of GERD or BE between 2001 and 2008. Intraoperative complications, as well as early (within 30 days) and late complications were analyzed in detail.

4.4.2. Intraoperative and early surgical complications

Conversion was required in 1 case in the GERD group because of adhesions. Open splenectomy (requiring postoperative transfusion) was performed in 1 case in the BE group because of spleen bleeding. Intraoperative chest tube insertion was required in 1 case in the GERD group because of left-sided pneumothorax. Reoperation was not performed in either group in the early postoperative period. In the GERD group, 2 patients were given a total of 6 units of pRBC because of bleeding, and subcutaneous emphysema was detected in 1 case, which did not require further treatment.

4.4.3. Late surgical complications between 2001 and 2008

During the early and late follow-up in the GERD group, observation at the institution was required in 3 cases because of dysphagia and stenosis: in 1 case, the complaints of the patient resolved spontaneously, in 1 case, endoscopic foreign body retrieval was performed because of food bolus obstruction (in the early period), and in 1 case, endoscopic balloon dilation was performed (in the late period). Usually, a satisfactory result was achieved with dilation, and reoperation has not been required in our practice to date. Endoscopic follow-up described the appearance of ulcer in 2 cases in the GERD group, and in 2 cases, BE was developed. In 1 case, cardiac resection was needed because of erosion due to the implanted mesh 7 months after the surgery. In the BE group, esophageal dilation was performed because of dysphagia in 2 cases. There were no mortalities in either group.

	GERD 176 PATIENTS	NOTE	**BE 78 PATIENTS**	NOTE
INTRAOPERATIVE COMPLICATIONS				
CONVERSION	**1 (0.57%)**	ADHESION	**1 (1.28%)**	SPLEEN INJURY
PNEUMOTHORAX	**1 (0.57%)**		**0**	
EARLY POSTOPERATIVE COMPLICATIONS				
TRANSFUSION	**2 (1.14%)**		**1 (1.28%)**	
SUBCUTANEOUS EMPHYSEMA (MAJOR)	**1 (0.57%)**		**0**	
LATE POSTOPERATIVE COMPLICATIONS				
SEVERE DYSPHAGIA	**3 (1.71%)**		**2 (2.56%)**	
APPEARANCE OF ULCER	**2 (1.14%)**		**0**	
DEVELOPMENT OF BE	**2 (1.14%)**		**–**	
MESH EROSION	**1 (0.57%)**		**0**	
DEATH	**0**		**0**	

Table 7. Comparison of the surgical complications in patients subjected to surgery because of GERD or BE

4.5. ENDOSCOPIC TREATMENT OF SPONTANEOUS ESOPHAGEAL RUPTURE, A COMPLICATION DEVELOPED ON THE BASIS OF BE

In this section, we present the minimally invasive treatment strategy of spontaneous esophageal rupture (Boerhaave's syndrome), a rare condition associated with BE. A 53-year-old male patient with lower-third rectal adenocarcinoma (T2N1) was admitted. He was known to have gastroesophageal reflux disease complicated with Barrett's esophagus (intestinal metaplasia with low-grade dysplasia). On the second postoperative day after a low anterior rectal resection, forceful vomiting occurred and was followed by chest pain without clinical signs of esophageal perforation. The immediate chest x-ray revealed only a small amount of pleural effusion on the right. The follow-up chest x-ray (acquired 12 hours later), however, demonstrated an increase in the amount of the pleural effusion, and hydropneumothorax was developed. A contrast swallow with a water-soluble contrast agent confirmed the presence of a transpleural esophageal rupture (Figure 1). The immediate upper gastrointestinal endoscopy showed a mucosal rupture of 5 to 7 mm in length on the posterior wall of the esophagus, 4 cm above the gastroesophageal junction. The mucosal tear was successfully closed with 3 endoscopic clips (Olympus Quick Clip 2) (Figure 2). The endoscopic closure was

supplemented with right thoracic drainage, gastrostomy and catheter feeding jejunostomy. Eight days after the endoclip application, esophagography demonstrated no further leakage, and oral feeding could be resumed. There were no complications and the patient was eventually discharged 14 days after the endoscopic intervention. Control endoscopy showed only scar tissue at the site of the closed perforation with LGD of BE.

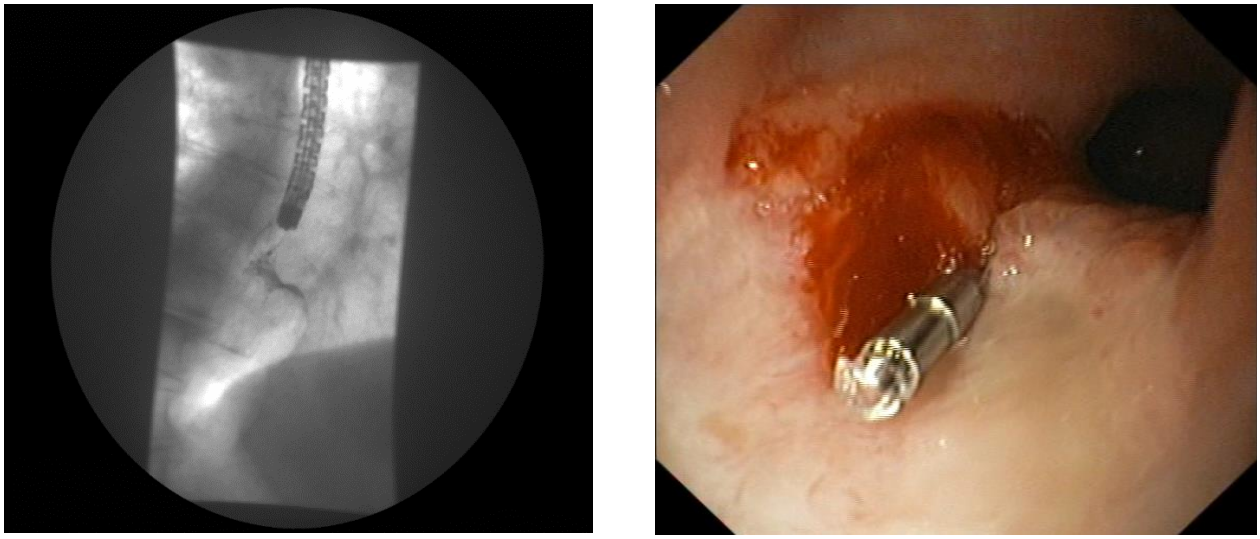


Figure 2. Left: The contrast material leakage site is to the left, above the cardia that slipped through the hiatal hernia. Right: Placement of an endoscopic clip to close the perforation

5. DISCUSSION

Reflux disease affects more than one third of the population, and it may range from an asymptomatic condition through a condition without inflammatory signs (non-erosive reflux disease) to a symptomatic condition accompanied by severe erosion and its complications that considerably worsen the quality of life. Parallel to this, the incidence of esophageal adenocarcinoma shows an increase in the developed world. In the presence of Barrett's metaplasia developed on the basis of reflux, the risk of developing esophageal adenocarcinoma is 30 to 125 times higher than in the normal population.[39,40]

5.1. ACID REFLUX, THE MOST LIKELY TRIGGERING FACTOR OF METAPLASIA

The pathomechanism of GERD involves (among other factors) changed dietary habits, overweight, increased abdominal pressure, and the anatomical defects (hiatal hernia) developed due to these, which increase the reflux that is already physiologically present by overcoming the barrier function of the cardiac region. Based on our preoperative assessment, patients were overweight in a considerable percentage and the prevalence of hiatal hernia was the same in the GERD and BE groups.

It has been known for a long time that in some cases, depending on the severity of the reflux, the acidic gastric contents regurgitating into the esophagus may cause symptoms only, whereas in other cases, they may damage the squamous epithelium lining the esophagus, resulting in erosion, inflammation and, later, ulceration and stricture.[5]

In the development of reflux esophagitis, at the microscopic level, the opening and widening of the gap between mucosal cells play a role. It was successfully triggered under experimental conditions with both mild and severe acid or mixed reflux.[41] At the site of the epithelial defect that is developed in case of persistent reflux, the regeneration starting from the submucosal pluripotent Schaffer glands may result in that columnar epithelium, which is more resistant to the acidic environment, replaces the squamous epithelium, i.e., Barrett's esophagus is developed. Its predictive factors are the total time of acid reflux, its severity and the consequentially worsening lower esophageal sphincter (LES) function.[13,42,43,44,45,46,47,48]

Our study supports the observation that the exposure to reflux is longer and more severe in the

group of patients with Barrett's metaplasia than in the group of patients with reflux alone. In our sample, however, no difference was found between the two groups in the duration of complaints and the LES impairment. Nevertheless, the mean history of 5.6 years is in accordance with the observation of Öberg who found that approximately the same time (6.2 years) is required for the columnar epithelial metaplasia to appear as a result of the increased exposure to acid. [49] It can be established, based on the above, that one of the most important factors in the squamous–columnar transformation is the appearance of acid in the esophagus.

This process theory is contradicted by the subgroup theory of Fass, according to which the different subgroups of GERD (non-erosive GERD, erosive GERD and complicated GERD) should be treated as separate entities, and there is only limited transition between them.[50] The difference between the uncomplicated GERD and BE subgroups appears to be confirmed also by molecular genetic studies, according to which the expression of a possible marker of dysplastic processes, the cdx-2 gene, can be detected both in the intact and in the metaplastic epithelium of patients in the BE group, whereas it is absent in the mucosa of patients with reflux alone.[51] According to this theory, reflux patients cannot be sorted into the same risk group with regard to the course of the disease, and there may be a difference also in the treatment strategy based on this.

5.2. DEVELOPMENT AND RISK FACTORS OF BARRETT'S ESOPHAGUS

The driving force behind the transition within the columnar epithelium and the appearance of intestinal metaplasia and dysplasia is the bile that is mixed with acid reflux. Bile acids that are in non-ionized but still solute form in the pH range of 3 to 5 of the acid mixed with the alkaline saliva in the esophagus are able to diffuse into the cells through the mucosal membrane, and return there to mostly ionized form at the intracellular pH, thus getting trapped and accumulating in the cells. Here, they may trigger the dysplastic processes by damaging the mitochondria of the cells. However, they may have a role not only in triggering carcinogenesis but also in the differentiation to adenocarcinoma. [13]

In the acidic–biliary environment, several "evolutionary responses" may appear often parallel to each other (fundic, cardiac and intestinal or even respiratory ciliary columnar epithelium, pancreatic acinar or ductal metaplasia, or low-grade, high-grade dysplasia or even in situ carcinoma). It is supposed that Schaffer glands have an important role in the development of

this diverse picture, because their pluripotent germ cells may be responsible for the heterogeneous responses to the inflammatory damage. [8] Besides the simultaneous presence of metaplasias, transformation into each other may also be supposed. Nevertheless, many of the above forms of metaplasia and dysplasia may be present in the mucosa even at the same time. [8]

A true risk of potential malignancy is associated with the appearance of IM.[28, 52] However, it is a known fact that the malignant transformation of non-intestinal epithelium cannot be excluded either, although its estimated risk is considerably lower (0.07% annually) than in the concomitant presence of intestinal metaplasia (0.38% annually).[28, 52] In other publications, the rate of dysplasia and carcinoma was almost the same in case of non-intestinal metaplasia than in IM. It must be added, however, that during the 5-year follow-up of this group, IM appeared in more than 50% of the cases, and this ratio reached 90% after 10 years.[53] It appears to support our conclusions below about the possible limitations of biopsy and the ability of metaplastic processes to transform into each other.

Although multiple biopsy samples may help assess the precise status of BE, only the momentary status of a small area can be assessed this way, which makes it hard to evaluate the efficacy of the treatment and the change in the condition. During the endoscopic examinations, multiple sampling is performed as per the Seattle protocol: on the one hand, from the visible Barrett lesions themselves, and on the other hand, from each esophageal quadrant with 2 cm intervals[26]. Increasing the number of biopsy samples clearly improves the ability to detect IM. According to the results of Harrison et al., with only 4 samples taken from the same patients, IM could be detected in only half of the IM cases previously confirmed with samples taken from 8 biopsy sites.[54]

In view of the above, we still consider it important, when Barrett’s esophagus is developed, not to focus only on intestinal metaplasias (that are confirmed to carry the potential for malignant transformation) but to follow non-intestinal (fundic and cardiac) metaplasias and other histological phenotypes as well.

In case of metaplasia or dysplasia, compared with patients with reflux disease alone, the presence of a larger hiatal hernia, more frequent LES insufficiency and more severe acid and bile reflux are assumed. Based on the above, the presence of a more frequent and more aggressive reflux is likely in tumorigenesis.[13, 28]

Additional risk factors may include old age, male gender, Caucasian race and overweight.[28] Smoking may also increase the risk. [28] Family history should also be assessed, since BE can be detected in almost one-fourth of the first-degree relatives of an individual with lower-third

esophageal adenocarcinoma. [28] Attention should be paid to this also when planning the follow-up and screening of patients.

In the clinical practice, long-term antacid treatment (with proton-pump inhibitors) is worth mentioning - it may even facilitate carcinogenesis in case of Barrett metaplasia because the achlorhydria developed in the stomach helps the bile acids reach the esophagus without precipitation, and the treatment may create a more favorable environment for the intracellular migration of bile acids by changing the pH in the distal segment of the esophagus.

Although the large meta-analyses have supported the trend only, it seems that the annual risk of developing adenocarcinoma is higher in the case of LSBE than in the case of SSBE. When comparing the two patient populations based on the length of BE, patients with adenocarcinoma had a significantly longer BE segment.[28] At the same time, the risk of esophageal cancer was lower in case of SSBE than in the other non-dysplastic BE groups. [28, 55]

The theory according to which bacterial colonization, and metabolites produced during bacterial metabolism, are potentially carcinogenic, was not supported by the Helicobacter pylori infection observed in the stomach. H. pylori infection was more common in patients with GERD (27% vs. 10%). It rather corresponds to the relatively low infection rate observed in BE by Nam et al., and correlates with the more common and more severe erosive reflux disease observed by them in the absence of H. pylori.[56]

The appearance of dysplasia and the length of BE further increase the risk of developing cancer. The presence of LGD means a 5- to 6-fold increase in the risk of malignant transformation (HGD and adenocarcinoma) compared with the non-dysplastic BE population.[28, 57] Based on the above, we suppose that a more severe acid-bile reflux has a pathogenic role in the development of dysplasia. Because of this, patients with BE in our study were assigned to three different groups based on the presence of conditions indicating carcinogenesis or its risk, depending on whether the histological sample taken during the endoscopy showed non-intestinal (i.e., fundic or cardiac) metaplasia (Group 1), intestinal metaplasia (Group 2) or low-grade dysplasia on the basis of the latter (Group 3). Taking into account that parallel metastatic and dysplastic conditions were likely in the biopsy samples, patients were always sorted based on the most severe condition found.

Patients with BE reported a mean duration of complaints of 5.6 years before the surgery. It was not different from the length of history reported by patients who underwent surgery because of GERD. There was no correlation between the severity of Barrett metaplasia (intestinal metaplasia and low-grade dysplasia) and the duration of complaints either and,

paradoxically, reflux complaints of longer duration were observed in the non-intestinal group, compared to the intestinal one. There were no differences in patient demographics (age, BMI, etc.) in the case of BE or, within this group, LGD.

When comparing patients who suffer from GERD with those who have BE, the more severe acid reflux confirmed in the BE group may cause metaplasia but a further role of acid reflux in the metaplasia–dysplasia transition in the BE subgroups could not be confirmed in the second half of our study. Nevertheless, our study showed that bile reflux was significantly more common and more severe in the low-grade dysplasia (LGD) group of BE patients than in the groups of patients with non-dysplastic metaplasia.[58]

Our hypothesis that changes in the anatomy of the gastroesophageal junction, a larger hiatal hernia or decreased LES pressure, decreased LES relaxation time, or a shorter LES, are more common in case of LGD, was not confirmed.

5.3. THE PLACE OF SURGERY IN THE TREATMENT OF REFLUX AND BARRETT'S ESOPHAGUS

In view of the above pathophysiology, it seems logical that restoring the impaired function of the GEJ may be the most effective treatment of the condition. But can we treat a disease that is mostly considered functional with a surgical procedure?

Conservative and surgical therapies are both accepted in the treatment of reflux, which has a central role in the development of the above mucosal transformation. With minimally invasive surgery becoming part of everyday practice, we can say that the morbidity risk of the laparoscopic antireflux surgery is low compared to its possible benefits to the patients.[59] The advantage of laparoscopic antireflux surgery over conservative therapy is that it attempts to restore the previous anatomical situation, i.e., it eliminates hiatal hernia by reconstructing the posterior diaphragmatic crus, restores the angle of His by retracting the lower portion of the esophagus into the abdomen, and restores the LES function with fundoplication. Unlike proton-pump inhibitors, it may eliminate not only acid reflux but also bile reflux. Compared with the permanent, lifelong medical treatment, it may be considered cost effective. However, opinions are divided on its long-term efficacy.[60, 61] A long-term complaint-free status can be expected in case of a correctly performed antireflux surgery. It can be established based in the

LOTUS trial that, regarding long-term efficacy, laparoscopic antireflux procedure is as effective as medical treatment. [62]

At the same time, the indications for laparoscopic antireflux surgery show considerable differences around the world. The practice of our department follows the SAGES guidelines.[63] Primarily, those reflux patients undergo surgery who do not respond to conservative therapy due to mixed or alkaline reflux, volume reflux, or a proximal reflux presenting with extraintestinal manifestation. The surgical solution may be preferred in young patients because of the need for permanent medical treatment, and in patients with poor compliance because of the frequency of relapses. Surgery is recommended also in the case of a large hiatal hernia accompanied by reflux. A further indication for surgery is if complications of GERD are developed. In the treatment of BE (one of the complications), surgery may be a treatment alternative that, besides eliminating the symptoms, may prevent the metaplasia - dysplasia - adenocarcinoma transition.

Our patients, therefore, had heterogeneous indications for surgery but the procedure was mostly performed after an unsuccessful conservative therapy. In our study, the patients in both groups underwent surgery after a mean 19 to 20 months of unsuccessful medical treatment. Our early postoperative functional examinations confirmed that laparoscopic antireflux surgery could achieve improvement, i.e., good reflux control, even in this presumably selected patient population with poorer prognosis and poorer response to conservative therapy (unsuccessful after a mean duration of one year and a half). LES pressure returned to the physiological range and the DeMeester score, which best describes acid reflux, decreased to normal values in both groups. Surgical treatment, therefore, may have additional advantages over medical treatment. Our results, however, must be considered to be of limited value because of the short follow-up of the functional examinations. Its mean duration did not exceed eighteen months in either group.

A further advantage of laparoscopic antireflux surgery is that it can be standardized, and therefore the steps of the procedure can be reconstructed later at any time, and the results from different institutions are comparable.[62] The arguments in favor of performing the surgeries in larger centers include - besides the high number of surgeries, which means adequate experience - the close cooperation between the surgeon and the gastroenterologist: at the time of making the correct indication for surgery and, naturally, during the implementation of the appropriate follow-up.[64, 65, 66]

Numerous studies have confirmed the advantages of the laparoscopic technique over the antireflux surgery performed with the conventional method. The question today is which of

the numerous laparoscopic antireflux procedures is more beneficial, what antireflux barrier we should create. Nissen's fundoplication creates a relatively stronger reflux barrier than partial fundoplication.[67] Dysphagia and also later dilation are more common in case of a 360-degree fundoplication but only among patients with decreased esophageal motility. In case of normal esophageal function, there is no difference between the two types of surgery. In case of total fundoplication, the "gas bloat" phenomenon is also more common.[68, 69] When comparing the partial anterior surgery and Nissen's fundoplication, dysphagia- and "gas formation"-related complaints are less common in case of anterior fundoplication, the reoperation rate is therefore also lower and, as a direct consequence, patients are more satisfied than after Nissen's procedure.[70] However, the recurrence of reflux symptoms (heartburn) and the need for restarting antacids is more common in this group, which suggests that Nissen's fundoplication may provide the best reflux control in the long term.[67, 68, 69, 70]

The closure strategy of larger hiatal hernias is also an important issue. Although hiatal hernia was common in both patient groups (69.32% and 64.1%), its mean size was only 3.5 and 3.73 cm, respectively and, therefore, a mesh was placed in a mere 5.5% of all cases. In these cases, the placement of the mesh was warranted by, besides the size of the hiatus, the unsuccessful tension-free closure of the diaphragmatic crura. To prevent the recurrence of hiatal hernia, we find it necessary to reinforce the diaphragmatic crura with a mesh in case of more than 3 diaphragmatic stitches. Primarily, the use of a PTFE or composite mesh secured with a spiral clamp and covering the diaphragmatic crura is recommended. In our practice, we preferably avoid wrapping the esophagus around completely. To prevent erosion caused by the mesh, besides the choice of material (Teflon or composite mesh), it was covered with the omentum in a few of our cases. Based on other publications, the ligamentum teres hepatis or the tensor fasciae latae muscle may also be used to reinforce or replace the mesh.[71, 72] Various allo- and xenografts may also be used in these cases.[72]

5.4. THE ROLE OF ANTIREFLUX SURGERY IN THE TREATMENT OF BARRETT'S ESOPHAGUS

BE may be treated with medical therapy, endoscopic ablation, antireflux surgery or a combination of these. The advantage of surgery over medical therapy is that by restoring the LES function, it eliminates not only acid reflux but bile regurgitation as well. Since the first

observation made by Brand et al.[73] (1980), it has become a generally known fact that antireflux surgery also creates an opportunity for the regression of BE. Based on the results of randomized and retrospective studies conducted to date, it can be established that antireflux surgery is more effective in preventing the progression of BE than medical treatment.[74, 75, 76, 77, 78, 79, 80, 81]

According to the most recent meta-analysis, antireflux surgery clearly has a beneficial effect on the regression of BE and dysplasia.[82] It has been found in some studies that surgery does not lead to an obvious decrease in the occurrence of adenocarcinoma, despite the excellent results published by numerous institutions about the beneficial effect of laparoscopic fundoplication in the treatment of reflux disease.[83, 84] According to a recent Swedish study, antireflux surgery does not prevent the development of esophageal or cardiac adenocarcinoma in some of the patients with GERD. [85]

The views on the role of antireflux surgery in prevention are quite contradictory in the literature. To date, no meta-analysis confirming or refuting a preventive effect with clear evidence has been published, and no large, prospective studies are expected in the near future either because of the special and small patient population.

Approaching the question from the perspective of the pathophysiology of the disease, a clear advantage of the surgical treatment is that, unlike the medical treatment, it may eliminate not only acid reflux, an important factor of the development of metaplasia, but also bile reflux, which is essential for provoking dysplasia.

This assumption seems to be confirmed by the fact that during the 42-month endoscopic follow-up of our patients subjected to surgery because of Barrett's esophagus, an unchanged status was observed in 53% of the cases, and regression was detected in a further 30%. Progression occurred in only 17%, and all of these cases were observed in the non-intestinal metaplasia group. Dysplasia was not developed in the group of patients with intestinal metaplasia, and no further progression (to high-grade dysplasia or carcinoma) occurred in the low-grade dysplasia group during the study period.

In the patient group showing regression, the postoperative functional results were significantly better than in the groups that did not show regression. However, we consider it important that the majority of our cases were short-segment BE. Based on the above, it can be established that in certain (presumably early) cases of BE, a laparoscopic antireflux surgery that provides effective reflux control may achieve regression even in patients not responding to medical treatment.

Csendes et al. [81] have reached a similar conclusion. According to our observations, laparoscopic antireflux surgery is associated with a low morbidity rate, and may decrease the

subjective complaints of short-segment BE patients in the long term (Visick Grade I and Grade II in 86.3 to 100% of the patients), it leads to the regression of intestinal metaplasia (IM) in one-thirds of the patients, and the IM does not progress to LGD, HGD or adenocarcinoma. In case of BE, surgical treatment should be considered also according to DeMeester et al., because they often observed the regression of LGD after antireflux surgery.[13] The regression of IM is more common in the group of patients treated surgically than in those who receive medical treatment.[82] A randomized study comparing the medical and surgical treatment has confirmed that a correctly performed antireflux surgery significantly decreases the rate of reflux esophagitis and stricture, and the segmental length of BE also significantly decreases after the surgery. [80] The rate of new-onset dysplasia was statistically different between the surgery group and the medically treated group (2% vs. 20%, respectively).[75, 86, 87, 88, 89] At the same time, the risk of malignant transformation was not lower than in the medically treated group. However, the same incidence of developing cancer in the two groups may be influenced by the fact that surgical treatment is performed in patients with more severe reflux - after medical treatment has failed.[86, 87, 89, 90] A preventive effect of laparoscopic antireflux surgery on the development of adenocarcinoma was not confirmed by the Swedish cohort study published by Lagergren et al. either.[91, 92] It must be noted, however, that this study compared the rate of adenocarcinoma with that in the healthy population and not in patients with reflux. [93] A “new-onset” BE developed after the antireflux surgery and the progression of an already present BE raise many concerns against the surgical treatment.

In the GERD patient group, the occurrence of metaplasia during our postoperative observation may have two explanations. The first is unsuccessful surgery. De novo BE may be expected in case of inadequate reflux control. It is contradicted by the fact that the results of our functional examinations did not differ from those observed in patients without progression. The second, more likely explanation lies in the limitation of biopsy already mentioned, that is, that the quadrant biopsy samples “taken blindly” in case of GERD provide a histological picture of a small area only, which does not exclude the prior presence of Barrett metaplasia in other areas, recognized only at the time of the second biopsy. Nevertheless, our opinion is that the clinical manifestation of BE should not be considered a uniform condition.

Although surgery that provides adequate reflux control can lead to regression (primary prevention) in a certain group of patients with BE, Barrett metaplasia was nonetheless observed after surgery in another patient group and, in a smaller portion of the patients, progression is not excluded either. Recognizing this patient group and following it more

closely are indispensable for secondary prevention, i.e., the early recognition and successful treatment of cancer.

The conclusion of DeMeester et al. may possibly explain progression - if carcinogenesis already started before the surgery because of the mixed reflux, and the meta- and dysplastic cells already got out of autoregulation control due to the genetic damages, the antireflux surgery, obviously, does not provide protection against advanced dysplastic processes, and in this case, adenocarcinoma may appear within 5 years after the surgery. In case of cancers developed later than this, they confirmed the recurrence of reflux.[13] Other studies[94, 95, 96] also point out that late adenocarcinoma following antireflux surgery can be explained by postoperative reflux due to an unsuccessful surgery or by recurrent reflux, and they emphasize the importance of pH-metry during follow-up.

It is also possible, however, that BE does not expose to a higher risk of developing adenocarcinoma but appears only as a coincidence. The fact that the histological examination confirmed BE next to adenocarcinoma in only half of the resections performed because of tumor may support this theory.[97, 98] Jamieson hypothesized that adenocarcinoma may be developed not or not only from the Barrett epithelium during tumorigenesis but the transformation of a pluripotent germ cell starts in response to inflammation and epithelial damage due to the reflux. [92] In this case, although the reflux-induced inflammation is also responsible for the development of BE, BE should be considered an indicator of the severity of reflux rather than a premalignant condition. The most likely case is that carcinogenesis does not occur in one way only, and dysplasia and cancer developed on the basis of BE is just one possible way in this process. Going ahead with this hypothesis, from the perspective of carcinogenesis, therefore, a successful antireflux surgery performed in time may be of preventive effect in certain patients with BE. Nevertheless, taking the slow progression of the condition and the great heterogeneity of BE into account, regular long-term endoscopic follow-up and biopsies are indispensable for the successful treatment of reflux disease and Barrett's esophagus. To confirm whether laparoscopic antireflux surgery can prevent the progression of Barrett's esophagus in the long term, repeat functional examinations to verify the effective functioning of the antireflux barrier are required besides endoscopic follow-up.

A further open question is the alternative long-term treatment of dysplastic (LGD) BE. Current recommendations consider only the need for endoscopic follow-up every six months confirmed. Although the efficacy of the treatment may be further improved by the ablation of the dysplastic epithelium, this is currently not recommended due to the lack of large randomized studies.[28] Numerous procedures are known for this, from the endoscopic

resection of the mucosa through radiofrequency ablation to laser, argon plasma coagulation, cryotherapy and photodynamic therapy. We should not forget, though, that a histological examination of the resected mucosa is performed and the exact depth of the dissection can be reconstructed only in case of endoscopic resections. In the rest of the procedures, there is less control of the ablation depth. The rate of potential complications (stricture and, more rarely, perforation) is also higher.[28] Special issues are invisible lesions and recurrence in the submucosal glandular structures, which, in case of LGD, may reach a rate close to 10% in the year following the procedure. We emphasize, nevertheless, that the procedures can be repeated. However, in knowledge of the pathomechanism of the disease, it is worth combining these procedures either with minimally invasive antireflux surgery or with permanent acid-reducing medical treatment, which may be completed with an NSAID in increased dose (300 mg Aspirin) for chemoprevention.[99]

5.5. MORBIDITY OF ANTIREFLUX SURGERY AND TREATMENT OF THE COMPLICATIONS OF BARRETT'S ESOPHAGUS

The minimally invasive surgical treatment performed at our center was an effective treatment alternative to unsuccessful medical treatment, without mortality and with a low morbidity rate. The conversion rate of 0.6 to 1.3% is considered low. The most common reasons for conversion include adhesions and injuries to adjacent organs. The most common perioperative complications, besides minor bleeding, are pneumothorax requiring pleural drainage and subcutaneous emphysema that can be controlled with conservative treatment. As to late complications, the most common is dysphagia that requires hospitalization (1.7 to 2.6%), which can be considered an "efficacy indicator" of Nissen's fundoplication. These cases often spontaneously resolve if adequate dietary instructions are given, and rarely need instrumental dilation. The most severe late complication is erosion of the esophageal wall after mesh placement (1.3%). Although it appears to be rare, its rate of 7.1% in patients with mesh placement only is high. Therefore, in our practice, besides the choice of material (Teflon or composite mesh), we avoid wrapping the esophagus around completely. To prevent erosion caused by the mesh, it was covered with an omental flap in a few cases. Other publications recommend the use of the ligamentum teres hepatis or the tensor fasciae latae muscle to reinforce or replace the mesh.[71, 72] Various allo- and xenografts may also be used in these cases.[72]

5.6. A RARE COMPLICATION OF BE - SPONTANEOUS ESOPHAGEAL PERFORATION

With the advance of surgical endoscopy, minimally invasive procedures have gained ground also in the treatment of the severe complications of BE. Their role in the diagnostics and therapy of both bleeding and obstruction is indisputable. Surgical treatment is required only in the rarest cases. A similarly rare severe complication is spontaneous perforation or Boerhaave's syndrome developed on the basis of BE ulcer. According to our knowledge, the closure of the perforation opening with endoscopic clips that we performed in our patient is the first documented successful case in Hungary.

The condition is the result of a pressure increase in the lumen of the esophagus, which is primarily caused by voluminous vomiting. Since our patient had known reflux disease complicated by BE with LGD, and esophagitis, a weakening of the distal esophageal wall could be assumed as well.

The condition was considered fatal until the first successful surgical treatment performed by Barrett in 1947. [100] Today, despite the more effective treatment options, mediastinitis and the rapidly developed septic condition are often irreversible. In cases where surgery is performed after more than 24 hours, the mortality rate exceeds 20 to 30%.[101]

The fundamental components of the treatment of esophageal rupture are the elimination of the septic source, the surgical or non-surgical closure of the defect, and thoracic and mediastinal debridement. Important parts of the therapy are the treatment of sepsis, intensive monitoring, targeted antibiotic/antifungal treatment, fluid therapy and increasing the ability of the body to resist by early enteral feeding. The treatment strategy is determined by multiple factors: the type of perforation (complete, intramural), its size, esophageal comorbidities, the time of making the diagnosis (delay), the presence of septic complications and the general condition of the patient. Choosing an individually tailored therapy requires considerable experience and availability of different therapeutic modalities.[102] According to literature data, the healing rate of primary esophageal suture completed with mediastinal and thoracic drainage exceeds 90% in cases where the esophageal injury is treated within 24 hours and is not complicated by other esophageal conditions (tumor, stricture, etc.).[103, 104]

In the past years, several cases of successful use of endoscopic clips and self-expanding stents in the treatment of esophageal rupture have been reported.[105, 106] Closure of an esophageal injury with endoscopically placed clips was first performed in 1995 (the injury occurred during pneumatic dilation in a patient with achalasia).[107] Since then, the method has been

used in esophageal perforations of several different etiologies, including Boerhaave's syndrome.[108, 109, 110, 111, 112] Currently, the procedure can be used in case of small injuries (< 1.5 cm) only. The method is suitable for the endoscopic closure of chronic spontaneous esophageal rupture and the consequential fistula.[113, 114] In our case, the complete esophageal perforation (with a rupture on the esophageal wall and also the mediastinal pleura) was detected within 24 hours. Since the visible rupture on the esophagus was only 5 to 7 mm, it could be successfully closed with endoscopic clips. Placing tubes surgically or with less invasive methods into the infected mediastinum and the chest, and debridement are indispensable for healing.

Endoscopic stents have been successfully used in the treatment of different types of esophageal perforation, including Boerhaave's syndrome.[115, 116, 117, 118, 119, 120]

It is well known that suture failure may occur also after the early primary surgical closure of esophageal rupture. Endoscopic clipping or stent placement may be useful therapeutic methods also in this case. Smaller defects can be treated and, therefore, more extensive surgical exploration can be avoided with their use.[121]

Based on the reports, the endoscopic placement of self-expanding stents is also a safe procedure associated with minimal mortality and morbidity rates.[122] The success of this procedure also depends on the early use of the method. Similarly to other therapeutic options, the chance of healing in case of esophageal perforation is considerably decreased by any delay in the endoscopic treatment.

The use of a minimally invasive technique has also appeared in the treatment of Boerhaave's syndrome.[123, 124] Avoiding thoracotomy, which is associated with a high rate of morbidity, may have considerable benefits for patients in severe condition. We know of several reported cases where a laparoscopic or thoracoscopic method was used in the treatment of spontaneous esophageal rupture.[123, 124, 125, 126, 127, 128, 129]

To summarize, we can establish based on the available experience that endoscopic and minimally invasive surgical methods, if proper conditions are met, may be therapeutic alternatives in the treatment of Boerhaave's syndrome developed on the basis of BE.

SUMMARY, OUR MOST IMPORTANT RESULTS

1. *The severity of the pathological acid reflux developed parallel to the incompetent functioning of the impaired lower esophageal sphincter potentiates, besides the inflammation in the lower third of the esophagus, the start of metaplastic processes and, ultimately, the development of Barrett's esophagus.*

2. *In response to the bile reflux accompanying the acid reflux, dysplastic changes may start in the metaplastic columnar epithelium (that appeared due to acid reflux).*

3. *In selected GERD and BE patients resistant to medical treatment, Nissen's correctly performed laparoscopic surgery can successfully control (eliminate or decrease) gastroesophageal reflux and is associated with a low morbidity rate.*

4. *The antireflux surgery may stop the progression of Barrett's esophagus and result in regression in some patients. Nevertheless, further long-term follow-up is required to confirm the assumed preventive effect of antireflux surgery in the process of carcinogenesis.*

5. *Endoscopic methods, if proper conditions are met, may be therapeutic alternatives in the treatment of esophageal perforation.*

ACKNOWLEDGEMENTS

First and foremost I wish to express my gratitude to my consultant, Prof. György Lázár for having been given the opportunity and for the ongoing support and tireless inspiration in my thesis.

I am particularly grateful to all members of the South Hungarian Regional Surveillance Group for the Study of Barrett's Esophagus for their constant help and support in the exemplary gastroenterologist-surgeon-pathologist cooperation.

I would like to offer my special thanks for his assistance in doing the statistics to Dr. Krisztina Boda and Ferenc Rárosi.

And I am obliged to all my young colleagues and medical students in the Department of Surgery without whom this work would have never been completed.

At last, but not at least I would like to express my gratitude for my family for their support and understanding.

Our study was sponsored by the Hungarian Research Fund, OTKA (grant K 73141), 340/09-ETT from the Hungarian Ministry of Social Welfare and the TÁMOP-4.2.2.A-11/1/KONV-2012-0035 projects.

REFERENCES

1. A Gallup Survey on Heartburn across America. (1988) Princeton NJ: The Gallup Organization.
2. Richter JE (1992) Surgery for reflux disease: reflections of a gastroenterologist. *N Engl J Med* 326(12):825-827.
3. Sonnenberg A, El-Serag HB (1999) Clinical epidemiology and natural history of gastroesophageal reflux disease. *Yale J Biol Med* 72:81-92.
4. Modiano N, Gerson LB (2007) Barrett's esophagus: Incidence, etiology, pathophysiology, prevention and treatment. *Ther Clin Risk Manag* 3(6):1035-1145.
5. Savarino E, Tutuian R, Zentilin P, Dulbecco P, Pohl D, Marabotto E et al. (2010) Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. *Am J Gastroenterol* 105(5):1053-1061.
6. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP et al. (1999) Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 45:172-180.
7. Vakil N, Zanten SV van, Kahrilas P, Dent J, Jones R, Global Consensus Group (2006) The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. *Am J Gastroenterol* 101:1900-1920.
8. Nemeth I, Rosztoczy A, Izbeki F, Roka R, Gecse K, Sukosd F et al. (2012) A renewed insight into Barrett's esophagus: comparative histopathological analysis of esophageal columnar metaplasia. *Dis Esophagus* 25:395-402.
9. Sharma P, Dent J, Armstrong D, Bergman JJ, Gossner L, Hoshihara Y et al. (2006) The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology* 131:1392-1399.
10. Shaheen NJ, Richter JE. (2009) Barrett's esophagus. *Lancet* 373:850-861.
11. Ronkainen J, Aro P, Storskrubb T, Johansson E, Lind T, Bolling-Sternervald E et al. (2005) Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 129:1825-1831.
12. Seidel D, Muangpaisan W, Hiro H, Mathew A, Lyratzopoulos G. (2009) The association between body mass index and Barrett's esophagus: a systematic review**.** *Dis Esophagus* 22:564-570.

13. T.R. DeMeester TR (2001) Clinical biology of the Barrett's metaplasia, dysplasia to carcinoma sequence. *Surg Oncol* 10(3):91-102.
14. Reid BJ, Levine DS, Longton G, Blount PL, Rabinovitch PS (2000) Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. *Am J Gastroenterol* 95:1669-1676.
15. Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RK, Vasudeva RS et al. (2003) Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology* 125:1670-1677.
16. Gerson LB, Shetler K, Triadafilopoulos G (2002) Prevalence of Barrett's esophagus in asymptomatic individuals. *Gastroenterology* 123:461-467.
17. Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S et al. (2008) Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. *Gut* 57:1354-1359.
18. Playford RJ (2006) New British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of Barrett's oesophagus. *Gut* 55(4):442.
19. Hayeck TJ, Kong CY, Spechler SJ, Gazelle GS, Hur C (2010) The prevalence of Barrett's esophagus in the US: estimates from a simulation model confirmed by SEER data. *Dis Esophagus* 23(6):451-457.
20. Voutilainen M (2008) Epidemiological trends in oesophageal cancer in the Nordic countries. *Scand J Gastroenterol* 43:323-327.
21. Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L (2008) The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: A systematic review and meta-analysis. *Am J Epidemiology* 168(3):237-249.
22. Garud SS, Keilin S, Cai Q, Willingham FF (2010) Diagnosis and management of Barrett's esophagus for the endoscopist. *Therap Adv Gastroenterol* 3(4): 227-238.
23. Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR (2005) Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann Surg* 242:566–573; Discussion 573-575.
24. Silny J (1991) Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. *J Gastrointest Motil* 3:151-162.
25. Rosztóczy A, Kovács L, Wittmann T, Lonovics J, Pokorny G (2001) Manometric assessment of impaired esophageal motor function in primary Sjögren's syndrome. *Clin Exp Rheumatol* 19:147-152.

26. Levine DS, Blount PL Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ (1993) An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* 105(1):40-50.
27. De Palma GD (2012) Management strategies of Barrett's esophagus. *World J Gastroenterol* 18(43):6216-6225.
28. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P (2014) British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 63:7-42.
29. DeMeester TR, Johnson LF, Joseph GJ (1976) Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 184:459-469.
30. Cuomo R, Koek G, Sifrim D, Janssens J, Tack J (2000) Analysis of ambulatory duodenogastroesophageal reflux monitoring. *Dig Dis Sci* 45:2463-2469.
31. Barrett MW, Myers JC, Watson DI, Jamieson GG (2000) Detection of bile reflux: in vivo validation of the Bilitec fibreoptic system. *Dis Esophagus* 13:44-50.
32. Tack J, Bisschops R, Koek G, Sifrim D, Lerut T, Janssens J (2003) Dietary restrictions during ambulatory monitoring of duodeno-gastro-esophageal reflux. *Dig Dis Sci* 48: 1213-1220.
33. Róka R, Rosztóczy A, Izbéki F, Taybani Z, Kiss I, Lonovics J, Wittmann T (2005) Prevalence of respiratory symptoms and diseases associated with gastroesophageal reflux disease. *Digestion* 71:92-96.
34. Rosztóczy A, Kovács L, Wittmann T, Lonovics J, Pokorny G (2001) Manometric assessment of impaired esophageal motor function in primary Sjögren's syndrome. *Clin Exp Rheumatol* 19:147-152.
35. Rosztóczy A, Róka R, Várkonyi TT, Lengyel C, Izbéki F, Lonovics J, Wittmann T (2004) Regional differences in the manifestation of gastrointestinal motor disorders in type 1 diabetic patients with autonomic neuropathy. *Z Gastroenterol* 42:1295-1300.
36. Richter JE, Blackwell JN, Wu WC (1987) Esophageal manometry in 95 healthy adult volunteers. *Dig Dis Sci* 32:583-592.
37. Rijnhart-De Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG (2008) The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol* 43:787-793.
38. Littell RC, Milliken GA, Stroup WW, Wolfinger, RD, Schabenberger O. (2006), SAS for Mixed Models, Second Edition, Cary, NC: SAS Institute Inc.
39. Cameron AJ, Lomboy CT (1992) Barrett's esophagus: age, prevalence, andextent of columnar epithelium. *Gastroenterology* 103:1241-1245.

40. Barrett's Esophagus: Cancer of the Esophagus. http://pathology2.jhu.edu/beWeb/Definition.cfm [Definiton]. [Copyright © 2000-2014 Johns Hopkins University]; [Accessed: 05 October 2015]
41. Farré R, Fornari F, Blondeau K, Vieth M, De Vos R, Bisschops R et al. (2010) Acid and weakly acidic solutions impair mucosal integrity of distal exposed and proximal non-exposed human oesophagus. *Gut* 59(2):164-169.
42. Clark GWB, Ireland AP, Chandrasoma P, DeMeester TR, Peters JH, Bremner CG. (1994) Inflammation and metaplasia in the transitional epithelium of the gastroesophageal junction – a new marker for gastroesophageal reflux disease. *Gastroenterology* 106:A63.
43. DeMeester TR, Ireland AP (1997) Gastric pathology as an initiator and potentiator of gastroesophageal reflux disease. *Dis Esophagus* 10:1-8.
44. Chandrasoma PT, Lokuhetty DM, DeMeester TR, Bremmer CG, Peters JH, Oberg S et al. (2000) Definition of histopathologic changes in gastroesophageal reflux disease. *Am J Surg Pathol* 24:344-351.
45. Bremner CG, Lynch VP, Ellis HF (1970) Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. *Surgery* 68:209-216.
46. Gillen P, Keeling P, Byrne PJ, West AB, Hennessy TP (1988) Experimental columnar metaplasia in the canine esophagus. *Br J Surg* 75:113-115.
47. Oberg S, Peters JH, DeMeester TR, Chandrasoma P, Hagen JA, Irelanad AP et al. (1997) Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastroesophageal reflux disease. *Ann Surg* 226:522-532.
48. Csendes A, Maluenda F, Braghetto I, Csendes P, Henriquez A, Quesada MS (1993) Location of the lower esophageal sphincter andthe squamous columnar mucosal junction in 109 healthy controls and 778 patients with different degrees of endoscopic esophagitis. *Gut* 34:21-27.
49. Öberg S, Johansson J, Wenner J, et al. (2001) Metaplastic columnar mucosa in the cervical esophagus following esophagectomy. In: Öberg S, (Editor): The columnar lined esophagus. Pathophysiological and clinical aspects. Bulletin No. 117, Department of Surgery, Lund University, Sweden.
50. Fass R, Ofman JJ (2002) Gastroesophageal reflux disease--should we adopt a new conceptual framework? *Am J Gastroenterol* 97(8):1901-1909.

51. Huo X, Zhang HY, Zhang XI, Lynch JP, Strauch ED, Wang JY et al. (2010) Acid and bile salt-induced CDX2 expression differs in esophageal squamous cells from patients with and without Barrett's esophagus. *Gastroenterology* 139(1):194-203.
52. Bath S. (2011) Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Nat Cancer Inst* 103:1049-1057.
53. Gatenby PA. (2008) Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined oesophagus. *Scan J Gastroenterol* 43: 524-530.
54. Harrison R, Perry I, Haddadin W, McDonald S, Bryan R, Abrams K et al. (2007) Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggest the nedd for minimum of eight biospies. *Am J Gastroenterol* 102: 1154-1161.
55. Desai TK, Krishnan K, Samala N, Singh J, Culey J, Perla S et al. (2012) The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis *Gut* 61: 970-976.
56. Nam SY. (2011) Helicobacter pylori Has an Inverse Relationship With Severity of Reflux Esophagitis. *J Neurogastroenterol Motil* 17: 209–210.
57. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. (2011) Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 365: 1375-1383.
58. Simonka Zs, Paszt A, Ábrahám Sz, Pieler J, Tajti J, Tiszlavicz L et al. (2012) The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. *Scand J Gastroenterol* 47:13-21.
59. Bálint A, Máté M, Barta T, Fazekas T, Solymosi A, Szabó K. (2001) [Antireflux procedures at our unit (1990–1999)]. [Article in Hungarian]. *Magy Seb* 54: 283–6.
60. Wilshire CL, Watson TJ. (2013) Surgical management of gastroesophageal refl ux disease. *Gastroenterol Clin North Am* 42: 119-131.
61. Bello B, Herbella FA, Allaix ME, Patti MG. (2012) Impact of minimally invasive surgery on the treatment of benign esophageal disorders. *World J Gastroenterol* 18: 6764-6770.
62. Galmiche JP, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S et al. (2011) Laparoscopic antirefl ux surgery vs. esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 305: 1969–1977.
63. Guidelines for Surgical Treatment of Gastroesophageal Reflux Disease (GERD). http://www.sages.org/publications/guidelines/guidelines-for-surgical-treatment-of-

gastroesophageal-reflux-disease-gerd/. Accessed: 17 March 2014. [Copyright © 2010–2014. Society of American Gastrointestinal and Endoscopic Surgeons].

64. Sandbu R, Sundbom M. (2010) Nationwide survey of long-term results of laparoscopic antirefl ux surgery in Sweden. Summary of consensus document on surgical procedures (LOTUS Trial). *Scand J Gastroenterol* 45:15-20.
65. Vakil N, Shaw M, Kirby R. (2003) Clinical effectiveness of laparoscopic fundoplication in a U.S. community. *Am J Med* 114:1-5.
66. Thibault R, Coron E, Sébille V, Sacher-Huvelin S, Bruley des Varannes S, Gournay J et al. (2006) Anti-refl ux surgery for non-erosive and erosive refl ux disease in community practice. *Aliment Pharmacol Ther* 24: 621-632.
67. Shan CX, Zhang W, Zheng XM, Jiang DZ, Liu S, Qiu M. (2010) Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. *World J Gastroenterol* 16:3063-3071.
68. Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. (2004) Evidence-based appraisal of antirefl ux fundoplication. *Ann Surg* 239:325-337.
69. Shaw JM, Bornman PC, Callanan MD, Beckingham IJ, Metz DC. (2010) Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. *Surg Endosc* 24:924-932.
70. Broeders JA, Roks DJ, Jamieson GG, Devitt PG, Baigrie RJ, Watson DI. (2012) Five-year outcome after laparoscopic anterior partial versus Nissen fundoplication: four randomized trials. *Ann Surg* 255:637-642.
71. Varga G, Cseke L, Kalmár K, Horváth OP. (2004) Prevention of recurrence by reinforcement of hiatal closure using ligamentum teres in laparoscopic repair of large hiatal hernias. *Surg Endosc* 18:1051-1053.
72. Horváth OP. (2010) The use of mesh in the surgical treatment of hiatal hernias. [Article in Hungarian]. *Magy Seb* 2010; 63: 312-315.
73. Brand DL, Ylvisaker JT, Gelfand M, Pope CE. (1980) 2nd. Regression of columnar esophageal (Barrett's) epithelium after anti-reflux surgery. *N Engl J Med* 302(15):844-848.
74. Gurski RR, Peters JH, Hagen JA, DeMeester SR, Bremner CG, Chandrasoma PT et al. (2003) Barrett's esophagus can and does regress after antireflux surgery: a study of prevalence and predictive features. *J Am Coll Surg* 196(5):706–12; Discussion 712-713.

75. Parrilla P, Martinez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J et al. (2003) Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. *Ann Surg* 237:291-298.

76. Rossi M, Barreca M, de Bortoli N, Renzi C, Santi S, Gennai A et al. (2006) Efficacy of Nissen Fundoplication Versus Medical Therapy in the Regression of Low-Grade Dysplasia in Patients With Barrett Esophagus: A Prospective Study. *Ann Surg* 243(1):58-63.

77. DeMeester SR, Campos GMR, Demeester TR, Bremner CG, Hagen JA, Peters JH et al. (1998) The impact of an antireflux procedure on intestinal metaplasia of the cardia. *Ann Surg* 228:547-556.

78. Desai KM, Soper NJ, Frisella MM, Quasebarth MA, Dunnegan DL, Brunt LM. (2003) Efficacy of laparoscopic antireflux surgery in patients with Barrett's esophagus. *Am J Surg* 186:652-659.

79. Abbas AE, Deschamps C, Cassivi SD, Allen MS, Nichols FC III, Miller DL et al. (2004) Barrett's esophagus: the role of laparoscopic fundoplication. *Ann Thorac Surg* 77: 393-396.

80. Biertho L, Dallemagne B, Dewandre JM, Jehaes C, Markiewicz S, Monami B et al. (2007) Laparoscopic treatment of Barrett's esophagus: long-term results. Surg Endosc 21(1):11-15.

81. Csendes A, Braghetto I, Burdiles P, Smok G, Henríquez A, Burgos AM. (2009) Late results of the surgical treatment of 125 patients with short-segment Barrett esophagus. *Arch Surg* 144(10):921-927.

82. Chang EY, Morris CD, Seltman AK, O'Rourke RW, Chan BK, Hunter JG et al. (2007) The Effect of Antireflux Surgery on Esophageal Carcinogenesis in Patients with Barrett Esophagus. A Systematic Review. *Ann Surg* 246:11-21.

83. Fein M, Bueter M, Thalheimer A, Pachmayr V, Heimbucher J, Freys SM et al. (2008) Ten-year outcome of laparoscopic antireflux surgery. *J Gastrointest Surg* 12(11):1893-1899.

84. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B et al. (2006) Clinical results of laparoscopic fundoplication at ten years after surgery. *Surg Endosc* 20(1):159-165.

85. Lagergren J, Ye W, Lagergren P, Lu Y. (2010) The Risk of Esophageal Adenocarcinoma After Antireflux Surgery. *Gastroenterology* 138(4):1297-1301.

86. Spechler SJ. (1992) Comparison of Medical and Surgical Therapy for Complicated Gastroesophageal Reflux Disease in Veterans. *N Engl J Med* 326:786-792.

87. Katz D, Rothstein R, Schned A, Dunn J, Seaver K, Antonioli D. (1998) The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. *Am J Gastroenterology* 93(4): 536-541.
88. McCallum R, Polepalle S, Davenport K, Frierson H, Boyd S. (1991) Role of anti-reflux surgery against dysplasia in Barrett's esophagus. Gastroenterology 100 (Suppl): A121.
89. Zaninotto G, Rizzetto C. (2007) Surgical options and outcomes in Barrett's esophagus. *Curr Opin Gastroenterol* 23: 452-455.
90. Tran T, Spechler SJ, Richardson P, El-Serag HB. (2005) Fundoplication and the risk of oesophageal cancer in gastroesophageal reflux disease: a Veterans Affairs cohort study *Am J Gastroent* 100(5):1002-1008.
91. Löfdahl HE, Lu Y, Lagergren P, Lagergren J. (2013) Risk factors for esophageal adenocarcinoma after antirefl ux surgery. *Ann Surg* 257: 579-582.
92. Jamieson GG. (2007) Antireflux surgery, Barrett esophagus, and adenocarcinoma: there is still room for doubt. *Ann Surg* 246(1):22-23.
93. DeMeester SR. (2013) Antireflux surgery and the risk of esophageal adenocarcinoma: an antithetical view of the data from Sweden. *Ann Surg* 257: 583-585.
94. Lagergren J, Viklund P. (2007) Is esophageal adenocarcinoma occurring late after antireflux surgery due to persistent postoperative reflux? *World J Surg* 31(3):465-469.
95. O'Riordan JM, Byrne PJ, Ravi N, Keeling PW, Reynolds JV. (2004) Long-term clinical and pathologic response of Barrett's esophagus after antireflux surgery. *Am J Surg* 188(1):27-33.
96. Mabrut JY, Baulieux J. (2006) Barrett's oesophagus: place of antireflux surgery, *Ann Chir* 131(3):177-182. Epub 2006 Feb 17.
97. Sabel MS, Pastore K, Toon H, Smith JL. (2000) Adenocarcinoma of the esophagus with and without Barrett mucosa, *Arch Surg* 135(7):831-835; Discussion 836.
98. Zhang J, Chen XL, Wang KM, Guo XD, Zuo AL, Gong J. (2004) Barrett's esophagus and its correlation with gastroesophageal reflux in Chinese. *World J Gastroenterol* 1;10(7):1065-1068.
99. Inczefi O, Németh I, Izbéki F, Róka R, Gecse K, Tiszlavicz L et al. (2010) A Long-term follow-up mucosal cyclooxygenase-2 (COX-2) activity in patients with Barrett's metaplasia and aspirin treatment, *Gut* 59:(Suppl 3) p. A 116.
100. Barrett NR (1947) Report of a case spontaneous perforation of the esophagus successfully treated by operation. *Br J Surg* 35:216-218.
101. Attar S, Hankins JR, Suter CM, Coughlin TR, Sequeira A, McLaughlin JS (1990) Esophageal perforation: a therapeutic challenge. *Ann Thorac Surg* 50:45-51.

102. Lázár G Jr, Paszt A, Simonka Z, Bársony A, Abrahám S, Horváth G. (2011) A successful strategy for surgical treatment of Boerhaave's syndrome. *Surg Endosc* 25(11):3613-9. doi: 10.1007/s00464-011-1767-1. Epub 2011 Jun 11.
103. Lawrence DR, Ohri SK, Moxon RE, Townsend ER, Fountain SW (1999) Primary esophageal repair for Boerhaave's syndrome. *Ann Thorac Surg* 67:818-820.
104. Sabanath S, Eng J, Richardson J (1994) Surgical management of intrathoracic esophageal rupture. *Br J Surg* 81:863-865.
105. Fischer A, Thomusch O, Benz S, von Dobschuetz E, Baier P, Hopt UT (2006) Nonoperative treatment of 15 benign esophageal perforations with self-expandable covered metal stents. *Ann Thorac Surg* 81:467-472.
106. Johnsson E, Lundell L, Liedman B (2005) Sealing of esophageal perforation or ruptures with expandable metallic stents: a prospective controlled study on treatment efficacy and limitations. *Dis Esophagus* 18:262-266.
107. Wewalka FW, Clodi PH, Haidinger D (1995) Endoscopic clipping of esophageal perforation after pneumatic dilation for achalasia. *Endoscopy* 27:608-611.
108. Cipolletta L, Biano MA, Rotondano G, Marmo R, Piscopo R, Meucci C (2000) Endoscopic clipping of perforation following pneumatic dilation of esophagojejunal anastomotic strictures. *Endoscopy* 32:720-722.
109. Raymer GS, Sadana A, Campbell DB, Rowe WA (2003) Endoscopic clip application as an adjunct to closure of mature esophageal perforation with fistulae. *Clin Gastroenterol Hepatol* 1:44-50.
110. Shimizu Y, Kato M, Yamamoto J, Nakagawa S, Komatsu Y, Tsukagoshi H et al. (2004) Endoscopic clip application for closure of esophageal perforations caused by EMR. *Gastrointest Endosc* 60:636-639.
111. Sriram PV, Rao GV, Reddy ND (2006) Successful closure of spontaneous esophageal perforation (Boerhaave's syndrome) by endoscopic clipping. *Indian J Gastroenterol* 25:39-41.
112. Qadeer MA, Dumot JA, Vargo JJ, Lopez AR, Rice TW (2007) Endoscopic clips for closing esophageal perforations: case report and pooled analysis. *Gastrointest Endosc* 66:605-611.
113. Raymer GS, Sadana A, Campbell DB, Rowe WA. (2003) Endoscopic clip application as an adjunct to closure of mature esophageal perforation with fistulae. *Clin Gastroenterol Hepatol* 1:44-50, 2003.

114. Sriram PV, Rao GV, Reddy ND. (2006) Successful closure of spontaneous esophageal perforation (Boerhaave's syndrome) by endoscopic clipping. *Indian J Gastroenterol* 25:39-41, 2006.
115. Bisgaard T, Wojdemann M, Heindorff H, Svendsen LB. (1997) Nonsurgical treatment of esophageal perforations after endoscopic palliationin advanced esophageal cancer. *Endoscopy* 29:155-159.
116. Chambers AS, Jordan T, McGranahan T, Kiev JA. (2005) A new management approach for esophageal perforation. *J Thorac Cardiovasc Surg*130:1470-1471.
117. Dormann AJ, Wigginghaus B, Deppe H, Huchzermeyer H. (2001) Successful treatment of esophageal perforation with a removable self-expanding plastic stent. *Am J Gastroenterol* 96:923-924.
118. Liedman B, Johnsson E, Lundell L. (2001) Treatment of iatrogenic perforations with covered stents in patients with esophageal cancer. *Eur J Surg*167:672-674.
119. Segalin A, Bonavina L, Lazzerini M, De Ruberto F, Faranda C, Peracchia A. (1996) Endoscopic management of inveterate esophageal perforations and leaks. *Surg Endosc* 10:928-932.
120. Serna DL, Vovan TT, Roum JH, Brenner M, Chen JC. (2000) Successful nonoperative management of delayed spontaneous esophageal perforation in patients with human immunodeficiency virus. *Crit Care Med* 28:2634-2637.
121. Fiscon V, Portale G, Fania P, Duodeci S, Frigo F, Migliorini G. (2008) Successful minimally invasive repair of spontaneous esophageal perforation. *J Laparoendosc Adv Surg Tech A* 18(5):721-722.
122. Johnsson E, Lundell L, Liedman B. (2005) Sealing of esophageal perforation or ruptures with expandable metallic stents: a prospective controlled study on treatment efficacy and limitations. *Dis Esophagus* 18:262-266.
123. Landen S, El Nakadi I. (2002) Minimally-invasive approach to Boerhaave's syndrome: a pilot study of three cases. *Surg Endosc* 16:1354-1357.
124. Scott HJ, Rosin RD (1995) Thoracoscopic repair of a transmural rupture of theesophagus. *J R Soc Med* 88:414-415.
125. Fiscon V, Portale G, Frigo F, Migliorini G, Fania PL. (2010) Spontaneous rupture of middle thoracic esophagus: thoracoscopic treatment. *Surg Endosc* 24(11):2900-2902.
126. Dapri G, Dumont H, Roman A, Stevens E, Himpens J, Cadiere GB. (2008) A delayed Boerhaave's syndrome diagnosis treated by thoracoscopy in proneposition. *Minerva Chir* 63:237-240.

127. Ashrafi AS, Awais O, Alvelo-Rivera M. (2007) Minimally invasive management of Boerhaave's syndrome. *Ann Thorac Surg* 83:317-319.

128. Vaidya S, Prabhudessai S, Jhawar N, Patankar RV. (2010) Boerhaave's syndrome: thoracolaparoscopic approach. *J Minim Access Surg* 6(3):76-79.

129. Toelen C, Hendrickx L, van Hee R. (2007) Laparoscopic treatment of Boerhaave's syndrome: a case report and review of the literature. *Acta Chir Belg* 107(4):402-404.